Abstract: The present invention relates to a stable ready-to-use pharmaceutical preparation of GLP-2 analogue for parenteral administration, wherein the preparation comprises GLP-2 analogue or its pharmaceutically acceptable salt thereof and pharmaceutically acceptable excipients; further the composition comprises of multi dose fixed dose and/or single dose injections through self-administrable devices.
READY TO USE COMPOSITIONS OF GLP-2 ANALOGUES THROUGH SELF-ADMINISTRABLE DEVICES

FIELD OF THE INVENTION

The present invention relates to a stable ready-to-use pharmaceutical preparation of GLP-2 analogue for parenteral administration, wherein the preparation comprises GLP-2 analogue or its pharmaceutically acceptable salt thereof and pharmaceutically acceptable excipients and the preparation are administered as multi-dose fixed dose and/or single dose injections through self-administrable devices.

BACKGROUND OF THE INVENTION

Glucagon-like peptide 2 (GLP-2) is a 33 amino acid peptide-encoded carboxyterminal to the sequence of GLP-1 in the proglucagon gene. Both GLP-1 and GLP-2 are secreted from gut endocrine cells and promote nutrient absorption through distinct mechanisms of action. GLP-2 regulates gastric motility, gastric acid secretion, intestinal hexose transport, and increases the barrier function of the gut epithelium. GLP-2 significantly enhances the surface area of the mucosal epithelium via stimulation of crypt cell proliferation and inhibition of apoptosis in the enterocyte and crypt compartments. Teduglutide, is a protease-resistant analog of GLP-2 for the potential treatment of gastrointestinal disease.

US7056886 patent publication disclose the h[Gly2]GLP-2 lyophilized formulation comprising in the reconstituted product: phosphate buffer in an amount necessary to maintain the pH of the reconstituted product pH of about 7.3 to about 7.4; about 0.5 to about 1% L-histidine; about 3% mannitol.

Teduglutide is commercially available as GATTEX® (teduglutide [rDNA origin]), single use glass vial which is a lyophilized formulation available as 5mg/vial sterile, white lyophilized powder for reconstitution with 0.5mL Sterile water for Injection provided in a prefilled syringe. In addition to the active pharmaceutical ingredient (teduglutide), each vial of GATTEX contains 3.88 mg L-histidine, 15 mg mannitol, 0.644 mg monobasic sodium phosphate.
monohydrate, 3.434 mg dibasic sodium phosphate heptahydrate as excipients. At the time of administration, the lyophilized powder is reconstituted with 0.5 mL of sterile water for Injection, which is provided in a prefilled syringe. Reconstitute each vial of GATTEX by slowly injecting 0.5 mL of preservative-free sterile water for Injection provided in the prefilled syringe. Allow the vial containing GATTEX and water to stand for approximately 30 seconds and then gently roll the vial between your palms for about 15 seconds. Do not shake the vial. Allow the mixed contents to stand for about 2 minutes. Inspect the vial for any undissolved powder. If undissolved powder is observed, gently roll the vial again until all material is dissolved. Do not shake the vial. If the product remains undissolved after the second attempt, do not use. It is for single-use only and discard any unused portion.

The commercially available teduglutide containing compositions are lyophilized and reconstituted before use, lyophilization of the drug is done to avoid the stability issues. Further the reconstituted compositions are not stable and must be used within 3 hours after reconstitution. It requires initial reconstitution, and the same needs to be carried out under aseptic conditions.

Considering the above drawbacks of the commercially available GATTEX product, it is difficult for a normal person to carry out the above described lengthy and tedious reconstitution process, further it needs to be carried out in a sterile environment, hence one need to avail expert services at hospital or clinics which will be expensive. Further if the lyophilized composition is undissolved after the second attempt, it needs to be discarded, which is again a loss to the patient administering the claimed composition.

In view of the above drawbacks of the commercially available GATTEX lyophilized product, the inventors have tried to overcome the above drawbacks and developed a stable ready to use liquid injection of GLP-2 analogue in a reservoir comprising a sterile solution administered through self-administrable
devices, wherein the GLP-2 analogue is dissolved in a pharmaceutically acceptable vehicle.

SUMMARY OF THE INVENTION

The present invention relates to a stable, ready-to-use pharmaceutical preparation of GLP-2 analogue for parenteral administration, wherein the preparation comprises GLP-2 analogue or its pharmaceutically acceptable salt thereof and pharmaceutically acceptable excipients.

The invention also relates to a stable ready-to-use pharmaceutical preparation of GLP-2 analogue for parenteral administration in a multiple dose or a single dose injection device comprising a sterile solution in a reservoir, wherein the GLP-2 analogue is dissolved in a pharmaceutically acceptable vehicle, wherein said reservoir comprises multiple doses or single dose of said sterile solution; wherein the device is adapted to subcutaneously inject a single daily dose or deliver multiple doses, while the solution remains sterile.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a stable, ready-to-use pharmaceutical preparation of GLP-2 analogue for parenteral administration, wherein the preparation comprises GLP-2 analogue or its pharmaceutically acceptable salt thereof and pharmaceutically acceptable excipients.

The present invention also comprises glepaglutide, a novel GLP-2 analogue with the potential to improve treatment of patients with short bowel syndrome. The present invention shall comprise of glepaglutide as a GLP-2 analogue for the treatment of short bowel syndrome (SBS).

The term "active ingredient" or "drug" refers to a substance that has a physiological effect when ingested or otherwise introduced into the body, in particular or a chemical substance used in the treatment, cure, prevention, or diagnosis of disease or used to otherwise enhance physical or mental well-being.
The term "excipient" or "pharmaceutically acceptable excipient" or "adjuvant" means a component of a pharmaceutical product that is not a pharmacologically active ingredient, such as diluent, bulking agent, carrier, acidifying agent, pH modifier, buffering agent, chelating agent, solvent, co-solvent, tonicity adjusting agent, antioxidant, preservative and the like added to a drug to increase or aid its effect. The excipients or adjuvants that are useful in preparing pharmaceutical compositions are generally safe, non-toxic, and neither biologically nor otherwise undesirable, and are acceptable for veterinary use as well as human pharmaceutical use. The term includes one or more excipients or adjuvants.

The term "preparation" or "composition" is intended to encompass a combination including active ingredients and pharmaceutically acceptable excipients, as well as any product which results, directly or indirectly, from combination, complexation, or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions involving one or more of the ingredients. The term "formulation" or "dosage form" or "composition" refers to finished pharmaceutical products that are suitable for administration, including, but not limited to, injections, etc.

The term "optional" or "optionally" means that the subsequently described element, component or circumstance may or may not be present, so that the description includes instances where the element, component, or circumstance is included and instances where it is not.

The term "stability" or "stable" as used herein includes both physical and chemical stability. Stability parameters include but not limited to potency, stable pH value and other physico-chemical parameters.

The term "self-administrable devices" as used herein includes administration of the preparation or composition or formulation by a person himself and/or without the intervention of other person. Self-administrable devices may include prefilled syringe, prefilled syringe with auto-injector, dual
chamber prefilled syringe, dual chamber cartridge with pen injection device, dual chamber cartridge with auto-injector, cartridge with pen injection device and the like.

"Carrier" or "vehicle" or "solvent" as used herein refers to pharmacologically inert materials that provide a more or less fluid matrix, suitable for topical drug administration. Carriers and vehicles useful herein include any such materials known in the art, which are nontoxic and do not interact with other components of a pharmaceutical formulation or drug delivery system in a deleterious manner. The formulations of the present invention are particularly suitable for parenteral administration. Formulations suitable for parenteral dosage forms such as injectable like intravenous, intramuscular or subcutaneous, implants and the like. Other parenteral ingredients used in the formulation are generally those commonly used and recognized by persons skilled in the art of parenteral formulations.

"Pharmaceutically-acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts, solvate, hydrate, esters and the like thereof. Pharmaceutically-acceptable salt forms of compounds provided herein are synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods.

The pharmaceutical preparation includes different GLP-2 analogues such as teduglutide or its pharmaceutically acceptable salt and the like, GLP-2 analogues as disclosed in US 5994500 A, US 5789379 A, US 9125882 B2 and US 6184201 B1, glepaglutide or its pharmaceutically acceptable salt and the like.

The pharmaceutical preparation further comprises of excipients such as tonicity adjusting agent, buffering agent, vehicle, carrier, pH modifiers, antioxidants, preservatives, chelating agents, bulking agents, diluents, surfactant, stabilizers and the like or mixtures thereof.
The pharmaceutical preparation, wherein, tonicity adjusting agent include but not limited to mannitol, sucrose, maltose, dextrose, trehalose, glycerin, sodium chloride, potassium chloride or mixtures thereof. Tonicity adjusting agents decrease the haemolysis of blood cells and reduce pain and irritation at the injection site.

According to the present invention, the amount of tonicity adjusting agent used in the said preparation is adjusted to obtain osmolality of the said preparation in the range of 290 to 330 mOsm/kg.

Examples of buffering agent include but not limited to acetate, citrate, tartrate, phosphate, benzoate, lactate, gluconate, bicarbonate, organic amines, its salts, hydrates, solvates, or any mixtures thereof.

Examples of vehicle or carriers include but not limited to water for injection, hydroalcoholic solvents like, propylene glycol, polyethylene glycol, ethanol, glycerol and mixtures thereof.

Examples of antioxidants include but not limited to monothioglycerol, L-cysteine, thioglycolic acid, sodium metabisulfite, ascorbic acid, sodium formaldehyde sulfoxylate, sodium bisulfate, butylated hydroxy toluene (BHT), butylated hydroxy anisole (BHA), phenylmercuric nitrate, thiomersal, benzalkonium chloride, benzethonium chloride, phenol, cresol or chlorobutanol.

Examples of preservatives include but not limited to benzyl alcohol, m-cresol, phenol, methyl parabens, propylparaben, butylparaben, chlorobutanol, thiomersal, phenylmercuric salts, or mixtures thereof. The sterile solution of the present invention comprises preservative in amounts sufficient to maintain sterility of the solution in the multiple dose pen injection device, throughout the shelf life of the product, which may be exposed to repeated multiple injections. This is because it is possible that the antimicrobial preservative concentration in a given preparation may decrease during the product's shelf life.

Examples of chelating agents include but not limited to ethylene diamine tetraacetic acid (EDTA) and acceptable salts thereof, citric acid, sodium citrate,
ethylene glycol-bis(beta-aminoethyl ether)-N,N,N',N'-tetraacetic acid (EGTA) and acceptable salts thereof, and 8-Amino-2-[(2-amino-5-methylphenoxy)methyl]-6-methoxyquinoline-N,N,N',N'-tetraacetic acid, tetrapotassium salt (QUIN-2) and acceptable salts thereof and the like or mixtures thereof.

Examples of stabilizers include but not limited to polyols, amino acids, surfactants, poloxamer and its co-polymers; polyols include but not limited to propylene glycol, polyethylene glycol, polypropylene glycol and the like or mixtures thereof; amino acids include but not limited to aspartic acid, glutamic acid, glycine, arginine, lysine, L-histidine and the like or mixtures thereof; surfactants include but not limited to polysorbate-20, polysorbate-80, and the like or mixtures thereof.

The pharmaceutical preparation, wherein the concentration of dose is in the range from about 2 mg/mL to about 200 mg/ml of the preparation.

The pharmaceutical preparation, wherein the device provides fixed dose as a multi dose pen injection device or a single dose injection device to give a fixed desired dose, as specified from about 2 mg/mL to about 200 mg/ml of the preparation.

The pharmaceutical preparation, wherein the device comprises of a reservoir comprising multiple doses of liquid injection or single dose quantity of injection to provide the desired dose.

Further, according to the present invention, the pH of the said pharmaceutical preparation is in the range of 2 to 9. For example, pH of the preparation is between about 7 to about 8.5.

In another aspect of the invention, there is provided a multiple dose pen injection device or a single dose injection comprising a reservoir of a sterile solution comprising teduglutide, tonicity adjusting agents, buffering agent, vehicle or carrier, antioxidant, stabilizer, and optionally preservative, the device being adapted to provide a portion of the reservoir directly from the multiple dose pen injection device in a single subcutaneous injection, said portion comprising
teduglutide in a pre-determined dose and the device further being adapted to provide multiple portions of the said solution while the reservoir remains sterile.

The present invention relates to self-administrable devices such as multiple dose pen injection device and/or independently a single dose reusable auto-injector device which has the provision to mount the ready to use prefilled syringes or suitable sterile container and/or reconstituted product filled in the prefilled syringe or suitable sterile containers to provide different fixed doses, comprising a sterile solution of teduglutide in a pharmaceutically acceptable vehicle. Reconstituted product refers to the lyophilized product upon reconstitution with sterile water for injection or other suitable diluent.

The sterile solution is present as reservoir; the device being adapted to subcutaneously inject a portion of the said reservoir as multiple dose pen injection or as a single daily dose of said solution while the reservoir remains sterile. Thus, suitably, the sterile solution is presented as a multiple dose preparation that is, the sterile reservoir of the solution that can be used for delivering multiple doses or as a single dose through a reusable auto-injector comprising a sterile solution either filled in a prefilled syringe or suitable sterile container and/or reconstituted product filled in the prefilled syringes or suitable sterile container. The reservoir of the sterile solution is present in the multiple dose pen device or prefilled syringe or suitable sterile container and a portion of that reservoir or container is withdrawn for each administration. The portion suitably contains a desired dose of teduglutide. The sterile solution of the present invention is meant for single dose administration as well. The sterile solution of the present invention optionally includes preservative in amounts sufficient to maintain sterility of the solution in the multiple dose pen injection device, throughout the shelf life of the product, which may be exposed to repeated, daily multiple injections. Suitable preservatives for the solution includes but are not limited to, benzyl alcohol, m-cresol, phenol, methyl parabens, propyl paraben, butyl paraben, chlorobutanol, thiomersal, phenyl mercuric salts, and the like. For
instance, when the solution contains benzyl alcohol as the preservative, it is present in an amount sufficient to maintain sterility of the solution in the multiple dose pen injection device, throughout the shelf life of the product, which may be exposed to repeated multiple injections.

In one embodiment, the multiple dose pen injection device comprises a reservoir filled with a solution of teduglutide, comprising a suitable preservative. The preservative containing solution is aseptically filtered (0.2-micron filter) and filled in pre-sterilized reservoir aseptically under sterile area. Suitably, there is no terminal sterilization step involved in the process. As the solution is intended for use as a multiple dose, it comprises teduglutide along with a preservative agent to keep the sterility maintained while being used multiple times throughout the shelf life of the product. Apart from a preservative, the pharmaceutically acceptable vehicle may comprise a buffer or tonicity adjusting agent. The pH of the solution is suitably adjusted to a pH range of 2 to 9. The pH may be adjusted using a suitable pH modifier. However, it is possible to use a buffer system to maintain the pH range. Suitable buffers that may be used include, but are not limited to acetate, citrate, tartrate, phosphate, benzoate, lactate, gluconate, bicarbonate, organic amines or any mixtures thereof and the like.

The sterile solution may optionally comprise other excipients known in the art to obtain a stable pharmaceutical preparation.

Generally, it is known that the preservative efficacy test (PET) is performed to evaluate the performance of a preservative. Such tests are described in literatures, such as for eg. Pharmacopoeias. The solution being suitable for multiple dosing, the PET may be performed. The sterile solution of the present invention being a multi dose preparation, it needs to maintain sterility during its shelf life that is while being used. Thus, the solution of the present invention in the multiple dose pen injection device, was subjected to in-use stability testing. The routine procedure provided by United States Food and Drug Administration (FDA), United States Pharmacopoeia (USP) and the European
Pharmacopoeia (EP) are followed to evaluate the sterility. The tests are PET (preservative Efficacy tests), sterility and BET (Bacterial Endotoxin Test).

An in-use shelf-life is intended to provide assurance of the appropriate quality of the product throughout its use, thereby ensuring the safety and efficacy of the product. The in-use shelf-life specified depends on the product, in particular its physical, chemical and microbiological characteristics. The in-use shelf-life is generally 28 days, however it may be less than this, for example if the active substance is prone to degradation following exposure to the atmosphere, or it may be longer than this, for example for a product which is very stable and which will not support the growth of micro-organisms (like some non-aqueous/oily injections). It is clear that during development of multi-dose sterile products it is necessary to carry out in-use studies to prove that a product remains physically and chemically stable and sterile during the in-use period.

According to one embodiment of the present invention, the sterile solution of teduglutide can be prepared by the following process which involves:

(i) required quantity of water for injection is taken in a vessel, to this required quantity of tonicity adjusting agent is added and stirred to dissolve.

(ii) suitable buffers, amino acid, optionally surfactant, antioxidant, optionally preservative, are added to the above solution followed by the addition of active ingredient teduglutide and stir to dissolve followed by pH adjustment of the solution.

(iii) sterilization of pharmaceutical solution of teduglutide by filtration using 0.2-micron filter; followed by aseptic filling of the solution under laminar flow into sterile containers. Further nitrogen purging is carried out as and when during the preparation process.

(iv) the step (iii) solution is optionally lyophilized in a dual chamber prefilled syringe to obtain a lyophilized cake or powder and water for injection is filled in other chamber.
The above described process is carried out at controlled temperature and during the process the nitrogen purging is carried out at required steps.

Another embodiment relates to preparation, wherein each ml comprises of teduglutide, arginine, mannitol, optionally poloxamer, optionally phenol or m-cresol, monothioglycerol, monobasic and dibasic sodium phosphate buffers, water for injection, and nitrogen gas is purged.

Another embodiment relates to preparation, wherein each ml comprises of teduglutide, L-histidine, mannitol, optionally polysorbate 80, optionally phenol or m-cresol, monothioglycerol, monobasic and dibasic sodium phosphate buffers, water for injection and nitrogen gas is purged.

The proposed preparations are presented as a single dose or multiple doses to provide the required doses, wherein, single dose is provided as a dual chamber prefilled syringe comprising two chambers, one chamber comprising the commercially available composition in lyophilized form and other chamber comprises of sterile water for injection. Other single dose preparation is provided as a ready to use composition in prefilled syringes, wherein, both the prefilled syringes are provided to fit into a re-usable auto-injector.

Multidose preparations are filled in cartridges to provide multiple doses of up to 28 doses through a pen injection device, after which the device shall get locked and cannot be used thereafter.

Each millilitre of the preparation comprises about 20 mg to about 50 mg of teduglutide with other excipients, which can be administered as a multiple dose. Multi dose preparations are presented in the sterile reservoir of the solution that can be used for delivering multiple doses or through a pen injection device comprising a sterile solution either filled in a cartridge or suitable sterile container.

Fill volume of preparation for multiple dose includes from about 0.05 ml to about 4.0 ml, for example between about 0.1 ml to about 3.5 ml.

Single dose preparation comprises 2 mg to 5 mg of teduglutide and can be administered as a prefilled syringe comprising a dual chamber reservoir.
comprising lyophilized preparation in one chamber and water for injection in another chamber and reconstituted before administration.

Further, single dose preparation shall also be administered as a ready to use composition comprised in a reusable auto- injector device.

Fill volume of preparation, includes from about 0.05 ml to about 4.0 ml, for example between about 0.1 ml to about 3.5 ml.

The pharmaceutical preparation, wherein the device provides predetermined fixed dose supplied as multi dose pen injection device, which has the provision to mount the ready to use prefilled syringes or suitable container and/or reconstituted product filled in the prefilled syringe or suitable containers to provide fixed desired doses.

Another embodiment provides a multi dose pen injection device and a method for administering a single predetermined dose of a solution containing teduglutide. The inventive device is having a reservoir containing a solution of teduglutide. The elongate, compact shape of the pen delivery device facilitates the use of simple pull-push handling techniques and allows the patient to easily carry the device on his/her person. The pen device is designed so that only a single predetermined dose is easily loaded by the patient using a pull-push technique of the device. The designed pen device is easy-to-use for all multi dose fixed dose therapies and the handling of device is simple and intuitive.

Simple pull-push technique is easy to handle and ensures a high level of patient convenience, loading a partial dose is not possible to avoid dosing errors. Suitable marking indicates whether the dose button needs to be pulled or pushed and the display is completely customizable. Also, the device indicates to the patient distinct and perceptible clicks to confirm whether the dose is loaded and also at the end of injection. Active last dose stop prevents the loading of a partial dose when the reservoir is nearly empty. Moreover, having only a single dose setting greatly reduces the possibility of a patient under dosing or overdosing himself or herself.
To further ensure that only a single accurate dose is delivered to the patient, the dosing sleeve of the pen device is calibrated and visibly marked with a single priming position indicator and a single predetermined injectable dose position indicator. This calibration and marking of the dose sleeve is a significant departure from existing pen delivery devices typically used for insulin, or human growth hormone delivery. Those existing devices are characterized in that they can deliver a great number of different dosages depending on where the patient or health care provider recommend dose. Moreover, the dose sleeve devices are marked and calibrated in International Units, having different possible predetermined dose settings. In contrast, the administration of teduglutide typically requires only a single, predetermined, non-varying dose on a daily basis.

Another embodiment relates to auto-injector in a self-contained, reusable multi use, preset and prefilled device configured to present a dosing choice to an end-user and to deliver a dose associated with the choice made by the end-user. As such, the auto-injector is configured to be capable of delivering a single dose chosen from a plurality of different doses of a pharmaceutical composition or medicament. In one aspect, the auto-injector is configured to be capable of delivering a single dose chosen from two different doses of a pharmaceutical composition or medicament. In other words, the device is capable of delivering different preset doses. The prefilled device may be a single chamber or a dual chamber, wherein single chamber may comprise of the ready to use preparation and a dual chamber may comprise of lyophilized composition in one chamber and diluent in other chamber.

The sterile solution filled prefilled syringe should be loaded into the reusable auto-injector device and ensure proper closure of the device to make ready for dosing. Before initiating next dose ensure the rigid needle shield should be removed or ejected form auto-injector device. After removing the needle shield the recorded dose is administered immediately. The working principle of the disclosed auto-injector device is similar or advanced to the auto-injector available in the general art.
The auto-injector is thereby configured to administer to a patient a pharmaceutical composition stored in a medicament reservoir disposed within it. The medicament reservoir cooperates with the dose selection component so that only the volume of pharmaceutical composition, at a given concentration corresponding to the selected dose is administered to the patient using the device. In one other embodiment, the medicament reservoir is a suitable device such as prefilled syringe and the like thereof, incorporated into the auto-injector housing, either permanent or removable.

Selection of the dose, either the higher dose or lower, yet already preset dose, is made by some form of manipulation of the injector such as by use of a button, slide, dial, shaking, audible/visible selection, or other input mechanism on the self-contained, single use, auto-injector. The injection device is calibrated so that only the amount of medicament that corresponds to the end-user dosage selection is dispensed from the reservoir and administered to the patient.

In another embodiment, the injection device is capable of accurately administering a full dose of a medicament or pharmaceutical preparation. Prior to administration or priming of the device may still be configured to be locked. The self-contained, single selectable dose auto-injector can be manufactured by providing a single selectable dose injector which has a selector. The selector can be actuated to dispense a single time, one of two pre-determined volumes of a liquid containing an active agent useful for treating the required condition.

Another embodiment relates to a single dose injection which can be administered by reusable single dose auto-injector device by mounting a prefilled syringe. Materials used for the preparation of prefilled syringe include but not limited to polypropylene, glass, plastics or polymers such as Cyclic olefin polymer (COP) or Cyclic olefin co-polymer (COC), polyethylene high density, polyethylene low density and the like or combinations thereof. Further other components for the prefilled syringe include barrel, plunger stopper, tip cap, plunger rod, lubricant, needle, needle shield cover, lock adapter, tamper evident, finger grip extender or back stop may be made of the material available in general art.
For dispensing a preset dose of a liquid drug includes two sleeve-like components releasably connected with each other so as to be aligned in axial direction. One of the sleeve-like components is a holder for a dispensing mechanism and the other of the sleeve-like components is adapted to accommodate a reservoir. The dispensing mechanism includes an axially movable plunger rod for actuating plunger of the reservoir. The plunger rod has a radially projecting cam follower and the holder defines at least one axially extending slot having a predetermined length, wherein the cam follower is received by at least one slot, such that only a single dose can be dispensed from a reservoir by an axial movement of the plunger rod.

Another embodiment relates to a delivery pen that houses reservoir assembly containing reservoir that has the capability of holding about a 60-day supply of daily doses of the pharmaceutical compositions described herein. In additional embodiments, the pen has the capability of holding a 1, 2, 3, 4, 5, 6, 7, or 8-weeks or more supply of daily doses of the pharmaceutical compositions described herein. Such a device provides ease of use for self-administration of the pharmaceutical compositions described herein.

In a further embodiment, the sterile container can contain a liquid dosage of the pharmaceutical composition, which is reconstituted by the user prior to injection. Those skilled in the pharmaceutical arts will recognize that medication delivery reservoir may be cartridge, prefilled syringe or suitable sterile containers assemblies and the like for holding the liquid comprising the pharmaceutical preparation.

In this embodiment, the reservoir containers were first pre-sterilized by an appropriate sterilization process and then the solutions were filled aseptically under sterile area. The material of construction of the reservoir containers can be either glass or plastic and the like. Depending upon the material, a suitable sterilization process can be adapted.

In another aspect, the present invention provides a method of administration of teduglutide to a subject in need thereof, said method comprising
daily subcutaneous administration of solution of teduglutide to the subject, wherein the solution is administered directly from the multiple dose pen injection device. This may be of particular importance in case of administration in children, where individualization for each child is necessary and the dose is based on mg/kg ratio of drug to body weight. The multiple dose pen injection device of the present invention imparts fixed dose of the medicament as well as the convenience of self-administration. The device thus provides an accurate and convenient method of administration of teduglutide which is not available in the art.

In a further embodiment of the injection device, the device is capable of offering the end-user a choice between a complete single dose or multi dose of the pharmaceutical preparation by using the auto-injector or multi dose pen injection device. A single dose is a predetermined volume of liquid containing the active agent at a fixed concentration, corresponding to essentially the entire reservoir volume of the device.

In another embodiment, the invention relates to the use of the GLP-2 analogues for treatment or prophylactic treatment of gastrointestinal disorders as well as stomach and intestinal-related disorders in a human or animal subject. Gastrointestinal disorders include the disorders of the upper gastrointestinal tract of the oesophagus. Stomach and intestinal-related disorders include ulcers of any aetiology (e.g. peptic ulcers, Zollinger-Ellison syndrome, drug-induced ulcers, ulcers related to infections or other pathogens), digestion disorders, malabsorptions, short bowel syndrome, cul-de-sac syndrome, inflammatory bowel diseases (Crohn's disease and ulcerative colitis), celiac sprue, hypogammaglobulinemic sprue, and chemotherapy and/or radiation therapy-induced mucositis and diarrhea. The disclosed preparations may be used alone or in combination with other therapeutic agents such as an anti-osteoporosis agent, hormones such as peptide hormone, steroid hormone or a non-steroid hormone, a bisphosphonate compound, growth hormone secretagogue, selective
estrogen receptor modulator, protease inhibitor, DPP IV antagonist or inhibitors and the like or any combinations thereof.

To further illustrate the invention, the following examples are provided. It is to be understood that these examples are provided for illustrative purposes and are not to be construed as limiting the scope of the invention. It is to be further understood that, in the examples the functions of individual ingredients are sometimes listed for illustration purposes.

Examples: Example 1 (Multidose preparation)

<table>
<thead>
<tr>
<th>Sl. No</th>
<th>Ingredients</th>
<th>TG1 Quantity (mg/mL)</th>
<th>TG2 Quantity (mg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Teduglutide</td>
<td>38</td>
<td>38</td>
</tr>
<tr>
<td>2.</td>
<td>L-histidine</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>3.</td>
<td>mannitol</td>
<td>114</td>
<td>114</td>
</tr>
<tr>
<td>4.</td>
<td>polysorbate 80</td>
<td>20</td>
<td>-</td>
</tr>
<tr>
<td>5.</td>
<td>poloxamer</td>
<td>-</td>
<td>20</td>
</tr>
<tr>
<td>6.</td>
<td>phenol</td>
<td>5.5</td>
<td>-</td>
</tr>
<tr>
<td>7.</td>
<td>m-cresol</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>8.</td>
<td>monothioglycerol</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>9.</td>
<td>monobasic sodium phosphate monohydrate</td>
<td>4.9</td>
<td>4.9</td>
</tr>
<tr>
<td>10.</td>
<td>dibasic sodium phosphate heptahydrate</td>
<td>26</td>
<td>26</td>
</tr>
<tr>
<td>11.</td>
<td>water for injection</td>
<td>q.s</td>
<td>q.s</td>
</tr>
<tr>
<td>12.</td>
<td>nitrogen</td>
<td>q.s</td>
<td>q.s</td>
</tr>
</tbody>
</table>

Manufacturing process:

(i) required quantity of water for injection is taken in a vessel, to this required quantity of mannitol is added and stirred to dissolve.

(ii) sodium phosphate buffers, L-histidine, polysorbate- 80 or poloxamer, phenol or m-cresol, monothioglycerol are added to the above solution followed by the addition of teduglutide and stir to dissolve followed by pH adjustment of the solution.
(iii) sterilization of pharmaceutical solution of teduglutide by filtration using 0.2-micron filter; followed by aseptic filling of the solution under laminar flow into sterile containers. Further nitrogen purging is carried out as and when during the preparation process.

Example 2: (Single dose preparation)

<table>
<thead>
<tr>
<th>Sl. No</th>
<th>Ingredients</th>
<th>TG3</th>
<th>TG4</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Teduglutide</td>
<td>3.8</td>
<td>3.8</td>
</tr>
<tr>
<td>2.</td>
<td>L-histidine</td>
<td>3.9</td>
<td>3.9</td>
</tr>
<tr>
<td>3.</td>
<td>mannitol</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>4.</td>
<td>polysorbate 80</td>
<td>0.7</td>
<td>-</td>
</tr>
<tr>
<td>5.</td>
<td>poloxamer</td>
<td>-</td>
<td>0.7</td>
</tr>
<tr>
<td>6.</td>
<td>monothioglycerol</td>
<td>0.16</td>
<td>0.16</td>
</tr>
<tr>
<td>7.</td>
<td>monobasic sodium phosphate monohydrate</td>
<td>0.16</td>
<td>0.16</td>
</tr>
<tr>
<td>8.</td>
<td>dibasic sodium phosphate heptahydrate</td>
<td>0.38</td>
<td>0.38</td>
</tr>
<tr>
<td>9.</td>
<td>water for injection</td>
<td>q.s</td>
<td>q.s</td>
</tr>
<tr>
<td>10.</td>
<td>nitrogen</td>
<td>q.s</td>
<td>q.s</td>
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</tbody>
</table>

Manufacturing process:

(i) required quantity of water for injection is taken in a vessel, to this required quantity of mannitol is added and stirred to dissolve.

(ii) sodium phosphate buffers, L-histidine, polysorbate- 80 or poloxamer, monothioglycerol are added to the above solution followed by the addition of teduglutide and stir to dissolve followed by pH adjustment of the solution.

(iii) sterilization of pharmaceutical solution of teduglutide by filtration using 0.2-micron filter; followed by aseptic filling of the solution under laminar flow into sterile containers. Further nitrogen purging is carried out as and when during the preparation process.
Example 3: (Single dose lyophilized preparation)

<table>
<thead>
<tr>
<th>Sl. No</th>
<th>Ingredients</th>
<th>TG3</th>
<th>TG4</th>
<th>Quantity (mg/mL)</th>
</tr>
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<tbody>
<tr>
<td>1.</td>
<td>Teduglutide</td>
<td>3.8</td>
<td>3.8</td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>L-histidine</td>
<td>3.9</td>
<td>3.9</td>
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<td>3.</td>
<td>mannitol</td>
<td>15</td>
<td>15</td>
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<tr>
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<td>monobasic sodium phosphate monohydrate</td>
<td>0.16</td>
<td>0.16</td>
<td></td>
</tr>
<tr>
<td>5.</td>
<td>dibasic sodium phosphate heptahydrate</td>
<td>0.38</td>
<td>0.38</td>
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</tr>
<tr>
<td>6.</td>
<td>water for injection*</td>
<td>q.s</td>
<td>q.s</td>
<td></td>
</tr>
</tbody>
</table>

"*" - water shall evaporate after lyophilization

Manufacturing process:

(i) required quantity of water for injection is taken in a vessel, to this required quantity of mannitol is added and stirred to dissolve.

(ii) sodium phosphate buffers, L-histidine, are added to the above solution followed by the addition of teduglutide and stir to dissolve followed by pH adjustment of the solution.

(iii) the above solution is lyophilized in a dual chamber prefilled syringe to obtain a lyophilized cake or powder and water for injection is filled in other chamber.

Although the invention herein has been described with reference to particular embodiments, it is to be understood that these embodiments are merely illustrative of the principles and applications of the present invention. It is therefore to be understood that numerous modifications may be made to the illustrative embodiments and that other arrangements may be devised without departing from the spirit and scope of the present invention as defined by the appended claims.
We Claim,

1. A stable ready-to-use pharmaceutical preparation of GLP-2 analogue for parenteral administration, wherein the preparation comprises GLP-2 analogue or its pharmaceutically acceptable salt thereof and pharmaceutically acceptable excipients.

2. A stable ready-to-use pharmaceutical preparation of GLP-2 analogue for parenteral administration in a multiple dose or a single dose injection device comprising a sterile solution in a reservoir, wherein the GLP-2 analogue is dissolved in a pharmaceutically acceptable vehicle, wherein said reservoir comprises multiple doses or single dose of said sterile solution; wherein the device is adapted to subcutaneously inject a single daily dose or deliver multiple doses while the solution remains sterile.

3. The pharmaceutical preparation according to claim 1 and claim 2, include different GLP-2 analogues such as teduglutide or its pharmaceutically acceptable salt thereof, excipients include: tonicity adjusting agent, buffering agent, vehicle, carrier, pH modifiers, antioxidants, preservatives, chelating agents, bulking agents, diluents, surfactant, and the like or mixtures thereof.

4. The pharmaceutical preparation according to claim 1 and claim 2, wherein the concentration of dose in the range from about 2 mg/mL to about 200 mg/mL of the preparation.

5. The pharmaceutical preparation according to claim 1 and claim 2, wherein the device provides fixed dose as a multi dose pen injection device or a single dose injection device to give fixed desired doses, as specified from about 2 mg/mL to 200 mg/mL of the preparation.

6. The pharmaceutical preparation according to claim 1 and claim 2, wherein the device comprises of a reservoir comprising multiple doses of liquid injection or single dose quantity of injection to provide the desired dose.

7. The pharmaceutical preparation according to claim 1 and claim 2, wherein the device comprises of a dual chamber prefilled syringe comprising, lyophilized
powder of teduglutide and other chamber comprises sterile water for injection to provide the desired dose.

8. The pharmaceutical preparation comprising the composition, injection device, and other excipients substantially as herein described and for treating teduglutide sensitive disease in mammals.
INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2018/050709

A. CLASSIFICATION OF SUBJECT MATTER
A61K38/00 Version=2018.01

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Patsee, IPO Internal Database, Totalpatent One

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>US8163696 B2 (ZEALAND PHARMA AS, 24 APRIL, 2012) abstract, column 30 line 59-67, column 27 line 20-56; column 29 line 8-10, column 30 line 47-49</td>
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<td>X</td>
<td>WO2001049314 A2 (NPS ALLELIX CORP, 12 JULY, 2001) abstract, page 3 line 5-9, page 9 line 4-7, example 1</td>
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<td>US7847061 B2 (SHIRE-NPS PHARMACEUTICALS INC, 07 DECEMBER, 2010) column 4, lines 50-64; column 5, lines 27-46, claims 1, 11-18</td>
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Further documents are listed in the continuation of Box C. See patent family annex.

Date of the actual completion of the international search | Date of mailing of the international search report
11-04-2018 | 11-04-2018

Name and mailing address of the ISA/Indian Patent Office
Plot No. 32, Sector 14, Dwarka, New Delhi-110075
Facsimile No.

Authorized officer
Ravi S
Telephone No. +91-1125300200

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