

Señor
Director de la Dirección de Nuevas Creaciones
Superintendencia de Industria y Comercio
Ministerio de Comercio, Industria y Turismo
E. S. D.

Re.: Expediente No. 12 077069
Solicitud de patente PCT, entrada en fase nacional, para:
**“COMPOSICIÓN FARMACÉUTICA QUE COMPRENDE UN AGONISTA DE GLP-1,
UNA INSULINA Y METIONINA”**
Solicitante: **SANOFI-AVENTIS DEUTSCHLAND GmbH**

RESPUESTA A SEGUNDO EXAMEN DE FONDO

Yo, **MARGARITA CASTELLANOS ABONDANO**, mayor de edad, identificada y domiciliada como aparece al pie de mi firma, obrando en mi calidad de apoderada de la sociedad solicitante del asunto citado en la referencia, en atención a su oficio No. **8287** notificado el **28 de junio de 2016**, atentamente me permito dar respuesta al mismo de la siguiente manera:

1. Modificaciones a las reivindicaciones

De acuerdo con lo establecido en el Artículo 34 de la Decisión 486 y en vista de las observaciones realizadas por el examinador, se presenta un nuevo pliego reivindicatorio conformado por cinco (5) reivindicaciones, en donde se han realizado la siguiente modificación:

- La reivindicación 6 referente a un kit de partes no se presenta en esta oportunidad.

Se solicita atentamente tener en cuenta este nuevo pliego reivindicatorio para el análisis de patentabilidad, toda vez que no implica una ampliación de la materia inicialmente solicitada y además permite superar las objeciones de claridad y concisión comunicadas por el examinador, cumpliendo así con los requerimientos del Artículo 30 de la Decisión 486.

2. Determinación del estado de la técnica

Para la evaluación de este requerimiento el examinador citó los documentos **D5**: US20080248999 y **D6**: CN 101444618.

3. Examen de patentabilidad

3.1. Nivel inventivo

Afirma el que examinador la persona del oficio normalmente versada en la materia incluiría metionina como lo describe el documento **D6** en la formulación divulgada en el documento **D5** para llegar así al objeto de la reivindicación 1 de la solicitud. Por lo cual considera que la solicitud es obvia.

Al respecto se desean resaltar los siguientes aspectos:

Como se comentó anteriormente en el memorial presentado como respuesta al examen de fondo 5997 (Radicado No. 12-077069-00007-0000 del 20 de Agosto de 2014), los datos experimentales de la presente solicitud, en particular las Figuras 1 a 3, evidencian que las formulaciones de lixisenatide (desPro³⁶ exendina-4(1-39)-Lys₆-NH₂) e insulina glargina (insulina humana Gly (A21)-Arg(B31)-Arg(B32)) que contienen metionina exhiben la menor cantidad de impurezas, en comparación con las formulaciones que no contienen metionina.

En relación al documento **D5**, como lo señaló el examinador, la presente solicitud se diferencia del documento **D5** (US 2008/0248999) porque el documento **D5** no divulga la presencia de metionina. Sin embargo, es importante señalar que el documento D5 tampoco menciona lixisenatide.

En relación al documento **D6**, no parece existir un equivalente en otro idioma diferente del chino para este documento, por lo tanto nuestros argumentos al respecto se referirán a la solicitud como fue citada por el examinador y a la traducción automatizada al inglés de la descripción¹ y de las reivindicaciones² obtenida de la página web de la Oficina Europea de Patentes por medio de la herramienta PatentTranslate (véase copia adjunta). De acuerdo con el análisis del examinador, la reivindicación 1 del documento **D6** se encuentra dirigida a una preparación farmacéutica que contiene un péptido de exenatida y metionina a un pH de 3,0 a 7,0. Sin embargo, como bien lo observa el examinador, el documento **D6** no describe lixisenatide o insulina glargina.

El documento **D6** divulga el papel de la metionina como antioxidante, de modo tal que la metionina estabiliza el contenido del péptido de exenatida en la formulación, como lo describe en el párrafo [0063], del cual se presenta a continuación una traducción al español con base en la traducción automática al inglés de la descripción (párrafo 4, pág. 6):

"[0063] Se obtienen las siguientes conclusiones con base en los resultados arriba mostrados (en referencia a los resultados de la Tabla 5: Contenido peptídico de las muestras almacenadas a 40°C por 4 semanas, analizadas semanalmente por RP-HPLC): La adición de azúcar (incluyendo glucosa, sacarosa, manitol) puede desempeñar un papel estabilizador en la exenatida; los surfactantes pueden reducir la formación de sustancias relacionadas; el EDTA no tiene efecto alguno sobre la estabilidad de la formulación; los amino ácidos tales como glicina o metionina dan estabilidad al producto, especialmente se observa la mejor protección para la formulación con metionina, la metionina en la formulación tiene un papel de regulación dual como antioxidante e isotónico, puede reducir el aumento de sustancias relacionadas, estabilizando así el contenido del péptido exenatida, por lo cual el sistema final preferido es el sistema de exenatida con metionina como accesorio. Teniendo en cuenta que la presión osmótica de la formulación inyectable debe ser cercana a la presión osmótica fisiológica, se selecciona la formulación con una concentración de metionina al 3% (p/v) como una dosis de preparación óptima."

[subrayado fuera del texto]

Se hace notar que no se puede deducir de esta descripción que la metionina también pueda estabilizar una formulación que contenga, además de lixisenatide, también insulina glargina.

Es importante destacar que la insulina glargina no contiene residuos de metionina en su secuencia de amino ácidos, cuya oxidación pudiera ser protegida por la metionina. De manera que, dicho efecto estabilizante no puede ser explicado por el efecto antioxidante de la metionina descrito en el documento **D6**. Hacemos notar que la exendina-4 si contiene residuos de metionina en su secuencia de amino ácidos (véase SEC ID N°: 2 en la página 6 de la solicitud), como se muestra a continuación.

¹ Descargada de: http://translationportal.epo.org/emtp/translate/?ACTION=description-retrieval&COUNTRY=CN&ENGINE=google&FORMAT=docdb&KIND=A&LOCALE=en_EP&NUMBER=101444618&OPS=ops.epo.org/3.1&S_RCLANG=zh&TRGLANG=en

² Descargada de: http://translationportal.epo.org/emtp/translate/?ACTION=claims-retrieval&COUNTRY=CN&ENGINE=google&FORMAT=docdb&KIND=A&LOCALE=en_EP&NUMBER=101444618&OPS=ops.epo.org/3.1&S_RCLANG=zh&TRGLANG=en

“La exendina-4 (39 AS) tiene la secuencia:
HGEFTFTSDLSKQMEEEEAVRLFIEWLKNGGPSSGAPPPS NH₂”
[subrayado y negrilla fuera de texto]

Adicionalmente, los datos divulgados en la presente solicitud muestran también que la cantidad de impurezas o productos de degradación de la insulina glargina puede disminuirse. En particular, la Figura 3 muestra el contenido de impurezas de insulina glargina después de 1 mes de almacenamiento a diferentes temperaturas (5 °C, 25 °C y 40 °C) a pH de 4 o 4.5. En la sección 7.2 del ejemplo 1, titulada “*Estabilidad después de 1 mes*” (véase págs. 38-40 de la solicitud), se describe la estabilidad química de la insulina glargina. Las formulaciones 3 y 4 son formulaciones de referencia para la insulina glargina. En la Figura 3, los valores de estas formulaciones de referencia se señalan con marcos estrechos. La figura evidencia que todas las formulaciones que se identificaron como las más estables en vista de las impurezas de lixisenatide (marco ancho), en particular, las formulaciones 25, 26, 28 y 30, son más estables que las formulaciones de referencia. **Por lo tanto, se puede concluir que la metionina permite una mayor estabilidad de almacenamiento para las formulaciones que contienen insulina glargina (y lixisenatide), la cual no puede ser explicado por el efecto antioxidante de la metionina descrito en el documento D6, puesto que como se mencionó anteriormente, la insulina glargina no contiene residuos de metionina, cuya oxidación pudiese ser protegida por la presencia de metionina.**

Con base en las anteriores observaciones, se evidencia que la persona del oficio normalmente versada en la materia no podría llegar a determinar el efecto de la metionina descrito en la presente invención sobre la base de las enseñanzas de los documentos **D5** y **D6**. En consecuencia, la reivindicación 1 tiene nivel inventivo a la luz del documento **D5** en combinación con el documento **D6**, cumpliendo así con el requisito establecido en el Artículo 18 de la Decisión 486.

4. No pago de nuevo examen de patentabilidad – Resolución 3719 de 2016

En esta oportunidad no se realiza pago por concepto de un nuevo examen de patentabilidad teniendo en cuenta que la presente solicitud fue publicada el 16 de octubre de 2012, y que en consecuencia ya ha caducado el plazo de 18 meses estipulado en la Resolución 3719 para solicitar un nuevo examen de patentabilidad.

5. Conclusión

Teniendo en cuenta las modificaciones introducidas en esta oportunidad y los argumentos que se presentan, es posible establecer que las reivindicaciones cumplen con los requerimientos de la Decisión 486.

6. **Anexos**

- Nuevo pliego reivindicatorio conformado por cinco (5) reivindicaciones.
- Traducción al inglés de la descripción del documento **D6**
- Traducción al inglés de las reivindicaciones del documento **D6**

Señor Director,



Margarita Castellanos Abondano
C.C. No. **39.779.654** de Bogotá
T.P.A. No. **70.819** del C.S.J.
Calle 94A No. 7A-09 - Bogotá, D.C.
Teléfono: 7560770

Bogotá, D.C.
MCA/nm
P2486
RESPUESTA EXAMEN DE SEGUNDO FONDO

REIVINDICACIONES MODIFICADAS EN RESPUESTA AL SEGUNDO**EXAMEN DE FONDO OFICIO 8287 – EXPEDIENTE 12 077069**

1. Una composición líquida que comprende un agonista GLP-1 y/o una sal farmacológicamente tolerable del mismo, una insulina y/o una sal farmacológicamente tolerable de la misma, caracterizada porque la composición líquida comprende L-metionina y tiene un valor de pH de 3,5 a 4,5, en donde el agonista GLP-1 es desPro³⁶exendina-4(1-39)-Lys₆-NH₂ y la insulina es insulina humana Gly(A21)-Arg(B31)-Arg(B32).
2. La composición líquida como se reivindica en la reivindicación 1, en donde la composición comprende un excipiente farmacéuticamente aceptable.
3. La composición líquida como se reivindica en la reivindicación 1, en donde la composición comprende un conservante farmacéuticamente aceptable y/o un agente de isotonicidad farmacéuticamente aceptable, en donde el conservante farmacéuticamente aceptable es m-cresol y el agente de isotonicidad farmacéuticamente aceptable es glicerol.
4. La composición líquida como se reivindica en la reivindicación 1, en donde la composición comprende metionina en una cantidad que varía de 0,5 mg/ml a 20 mg/ml, más particularmente en una cantidad que varía de 1 mg/ml a 5 mg/ml.
5. La composición líquida como se reivindica en la reivindicación 1, en donde la composición tiene los siguientes constituyentes:
 - (a) desPro³⁶exendina-4(1-39)-Lys₆-NH₂
 - (b) insulina humana Gly(A21)-Arg(B31)-Arg(B32)
 - (c) cloruro de cinc
 - (d) m-cresol (opcional)
 - (e) L-metionina
 - (f) Glicerol
 - (g) Ácido clorhídrico, si se requiere un ajuste de pH de aproximadamente 4,5
 - (h) Solución de NaOH, si se requiere un ajuste de pH de aproximadamente 4,5, y
 - (i) Agua.



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Notice

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DESCRIPTION CN101444618

The present invention discloses a pharmaceutical formulation comprising exenatide (exenatide is) a. The pharmaceutical preparations in addition to exenatide as an active ingredient, but also contains a buffer pH of about 3-7 10-100mm and accessories increase the stability of exenatide. Advantages of the present invention is that by adding some components that can be accepted by the human body, thereby preparing a kind suitable for clinical use, particularly for injectable use and stable preservation of Exenatide formulation.

Pharmaceutical formulations containing exenatide

Field of the Invention

The present invention relates to stable pharmaceutical formulation of exenatide, the pharmaceutical preparation can be used for patients with diabetes Treatment.

BACKGROUND

Exenatide (exenatide or exendin-4) from the first large Gila (Heloderma suspectum) Saliva secretion separated (Eng, J. Etc., J.Biol. Chem, 265: 20259-62,1990; Eng, J. Etc., J.Biol. Chem, 267: 7402-05,1992), which is a 39 amino acid polypeptide, Its amino acid sequence with the class of glucagon glucagon-like peptide-1 (GLP-1) with about 53% Endogenous (Goke etc., J.Biol. Chem, 268: 19650-55,1993), which amino acid sequences such as under:

His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu- Glu-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser- Ser-Gly-Ala-Pro-Pro-Ser

[152]

Pharmacology studies have found that exenatide and GLP-1 has a similar effect, which can stimulate pancreatic β cells Insulin secretion. Exenatide in vitro effect on GLP-1 subject to certain insulin-secreting cells on Body, acting on the spread and effect of acinar cells from guinea pig pancreas cells from the wall of the stomach; also reported the Peptides stimulate somatostatin release and inhibits gastrin release in isolated stomachs (Goke etc., J.Biol. Chem, 268: 19650-55,1993; Schepp, etc., Eur. J.Pharmacol, 69: 183-91,1994; Eissele, etc., Life Sci, 55: 629-34,1994). Exenatide significantly longer than the action of GLP-1 time (Prolonged effect of hyperglycemia Eng, J.exendin-4 Dui db / db mice (Prolonged effect of exendin-4 on hyperglycemia of db / db mice), Diabeteds 1996 Nian 5 months; 45 (Suppl 2): 152A (Abstract 554)).

Exenatide with human GLP-1 receptor binding and activation of the receptor, thereby facilitating the combination of insulin Into and secretion. Exenatide is a new molecular entity, which with other hypoglycemic agents structurally related to nothing Sex. Although exenatide showed a glucose-dependent manner stimulate insulin secretion, and insulin, but it does not structure Relevance, and there is no clinical evidence that it can be used as a substitute for insulin.

Exenatide-induced cAMP production on the basis of receptor systems in humans and rats and the role of GLP-1. Substantially the same, the most significant part of the receptor binding site of pancreatic islets. Exenatide found in perfused rat. It can promote the first-phase insulin secretion and second-phase insulin secretion. Cellular level studies have shown Mingyi Se. Exenatide and insulin in the case of absence of somatostatin can block the action of glucagon. This suggests Exenatide also play a role in the single cell level. Exenatide can also dose-dependently slowed gastric emptying rate. Reduction of food intake, acute exenatide injection may be dose-dependent to about 75% (in animals or humans are This phenomenon). In vivo, exenatide through a variety of mechanisms to improve fasting and postprandial blood Sugar concentration, suitable for long-term treatment of type 2 diabetes. The drug by the US Amylin and Eli Lilly companies to develop, FDA has approved its listing under the trade name Byetta, for the use of metformin alone. Guanidine, sulfonylureas or metformin and sulfonylurea combination therapy failed to achieve good control of type 2 diabetes. Patients with adjuvant therapy.

At home and abroad reported about exenatide (exendin-4) patent literature there are many, is hereby cited as follows:

Exenatide peptide as a drug or its stability can not be compared with conventional chemical drugs,

Its physical and chemical, biological properties due to be affected by a variety of environmental factors and changes in long-term storage.

example Such as highly sensitive to temperature, oxygen and ultraviolet light. Because of these factors, a variety of physical or chemical may occur. Histological changes, such as adsorption, polymerization and oxidation. Therefore, if the stability during storage can not be guaranteed exenatide. Then, it will lead to dose variations affecting efficacy. Since the injection of exenatide for clinical II Treating diabetes, the existing program is 5-10 micrograms per dose administered 2-3 times per day, week using. Period of up to six months or more. Therefore, the preparation of a stable form of preparation for the convenience of patients administered exenatide. Clinical application is extremely important. U.S. Patent (US6902744 and US7115569) discloses a method comprising Exenatide has the pharmaceutical composition prepared according to this patent the formulation (trade name: id = "102045507-idf0001" />) Has Pro Application of the bed. However, the pharmaceutical composition according to this patent are prepared to be stored at low temperature in order to maintain Stability certificate exenatide. In addition, in order to prevent pollution caused by the use of multi-dose and added preservatives. Moreover, the existing form preparations are still many problems in practical use, due to the stability problems, exenatide, Peptide agents need cryopreservation, the existing multi-dose packaging on the go is difficult to ensure low temperature storage conditions. Thus affecting the quality of medicines, thereby affecting efficacy; long-term use of products containing a preservative, it may bring More potential damage and the like.

Thus, we developed a stable saved exenatide, and pharmaceutical formulations suitable for practical clinical use. It is extremely significant. The present invention relates to is this aspect.

SUMMARY

Object of the present invention is to provide a stabilizing agent containing exenatide having good at room temperature Good stability, and preservative-free, with better security.

According to the clinical use of the characteristics of exenatide, the most secure form of injectable preparation is preferably a single dose package. Equipment, precise dosage, without potentially dangerous substances, stable at ambient temperature and easy to carry out and save. Because exenatide injection every clinical dose is extremely small, generally 5-10 micrograms per dose, and therefore the system Stabilized, facilitate the application of a single dose is extremely difficult. Exenatide as a peptide drugs, which often Low-temperature stability, and because clinical dose is small, the content of single-dose packaging Neiyi Se peptide that only 10 Micrograms, packaging equipment easily adsorbed by the walls. Even if the initial increase in the content of the package and no Exenatide Method to solve this problem, because the walls of the adsorber is time-dependent, can not be loaded by additional quantitative To make up for the amount of adsorption of the wall; on the other hand, for the convenience of the patient to carry and use, single dose packaging Asay Exenatide injection agent is preferably stable at room temperature, so that the patient can easily carry out and save it for external The use of traveling. According to the US Patent (US6902744 and US7115569) provided by pharmaceutical group Compound prescription, and can not fully achieve the effects mentioned above. For example, according to a single dose of the technical solution should be prepared With exenatide injections in the case of single-dose low (<20 micrograms / branch), in pre-filled syringe The preservation process changes over time, the content will gradually decline. Moreover, according to this aspect of the drug preparation By injection, at room temperature, the stability is limited, after a short time storage, which appears decreased, Related substances increase and so on. So far, there is no one technology solution that can make preparation for clinical It can be stored at room temperature in a single-use exenatide pharmaceutical formulation used.

The inventors of this study through a large number of formulation and stability testing, accidentally acquires a packet A pharmaceutical composition containing low concentrations of exenatide. Compared with the prior art solutions, the composition is greatly reduced The wall adsorption of exenatide, so that a single low dose preparation of specifications using exenatide injection may become can. Moreover, the inventors have also unexpectedly found that by stability test, according to the present invention is prepared exenatide injection Injection, compared with the prior art solutions, has better thermal stability, can be stored at room temperature for longer Time without affecting their content and quality, thereby facilitating the use of everyday diabetes, in particular of travel Between the carrying and use (see Example 2 comparison result).

In addition to pharmaceutical formulations of the present invention as an active ingredient exenatide, but also to maintain the formulation comprising a pH value of an aqueous solution pH 3.0-7.0 buffer and enhanced stability of exenatide materials, solution In the range of 3.0 to 7.0, preferably 4.0 to 6.0, most preferably pH 4.5. Advantage of the present invention is that by adding a These ingredients can be accepted by the human body, and enhance the physical and chemical stability and biological activity of exenatide to prepare A kind suitable for clinical use, especially in formulations for injectable use. Such formulations may prevent an active ingredient (AI Plug exenatide) due to the adsorption vessel, or because of degradation, oxidation and other factors lead to failure, thus facilitating transport, Long-term storage and clinical use.

[30]

Above pharmaceutical formulations, the concentration of exenatide in a liquid formulation of 10-500 μ g / ml, preferably 30-150 μ g / ml, and most preferably 50 μ g / ml.

[3]

The pharmaceutical formulations described above, the present invention is suitable for a buffer to maintain the formulation in an aqueous solution any one of a pH 3.0-7.0 buffer solution, optionally from disodium hydrogen phosphate - citric acid buffer, phosphate Buffer, acetate buffer, barbital buffer or sodium citrate buffer at a concentration of 5-100mmol / L, Preferably 10-30mmol / L, most preferably 20mmol / L; pH of the buffer in the range of 3.0 to 7.0, preferably 4.0 to 6.0, Most preferably pH 4.5. Wherein, the buffer is preferably a phosphate buffer, disodium hydrogen phosphate - citric acid buffer solution or Acetic acid - sodium acetate buffer, most preferably disodium hydrogen phosphate - citric acid buffer, at a concentration of 5-100mmol / L, preferably 10-30mmol / L, most preferred concentration is 20mmol / L, pH of the solution in the range of 3Between .0-7.0, preferably 4.0-6.0, most preferably pH 4.5.

Pharmaceutical formulations described above, the enhanced stability of the materials can be used exenatide methionine, glucose, Sucrose, mannitol, glycine, or one or more, preferably methionine. Methionine concentration (w / Solution volume, w / v) of 1% to 6%, preferably 2% to 4%, and most preferably 3%.

If necessary, can also be prepared in the above pharmaceutical preparation is freeze-dried powder, liquid formulation before freeze-drying group The upper and isotonic or isotonic, so after adding the right amount of water for injection lyophilized capable of reducing formation of sheets or the like Infiltration solution.

The present invention uses a disposable pre-filled syringes, vials or ampoules of this preparation as a storage container, Preferably pre-filled syringes, pre-filled syringe and most preferably from 1ml capacity, the advantage of easy to use, can be reduced Less pollution middle of the process, while in small doses, small volume injection liquid can be fully utilized to ensure that due And is particularly suitable for use of microinjection. Advantage of the present invention is that by adding some body can be accepted into Points, and enhance the physical and chemical stability of the biological activity of exenatide, thereby preparing a kind suitable for clinical make Use, especially in formulations for injectable use. Such formulations may prevent an active ingredient (exenatide) Since the container Adsorption, or degradation due to a variety of factors, such as oxidation and lead to failure, thus facilitating transport, preservation and long-term clinical use.

The present invention is applied to a buffer capable of maintaining the formulation is an aqueous solution at a pH of 3.0-7.0 Any of the buffers, such as phosphate buffer, acetate buffer, citrate buffer and sodium barbital buffer Wait. Presently preferred buffer is disodium hydrogen phosphate - citrate buffer, pH value is preferably 4.0-6.0, and most Preferably 4.5. In order to investigate the stability of the formulation under different pH conditions, the following conditions were different pH strips Member on formulation stability experiment:

By exenatide stability screening method under different pH conditions are as follows: Weigh exenatide, Dissolved in water to 10 μ g / 0.2ml exenatide and the solution was divided into 4 parts, each with different pH buffer Chong was adjusted to pH

3.5,4.5,5.5,6.5 with 1ml of pre-needle four kinds of pH of the solution were dispensed 0.2ml / Branch, and then placed in an oven at 40 ° C accelerated test for ten days to observe the product by HPLC method degradation, Table 1.

①pH = 3.5 (acetic acid - sodium acetate buffer), 20mmol / L

②pH = 4.5 (disodium hydrogen phosphate - citric acid buffer solution), 20mmol / L

③pH = 5.5 (disodium hydrogen phosphate - citric acid buffer solution), 20mmol / L

④pH = 6.5 (phosphate buffer), 20mmol / L

Detection exenatide injection by RP-HPLC method is as follows:

Apparatus: Column: Sepax C4 4.6 × 150mm (Sepax Technologies, Inc.)

Reagents: phosphate buffer (PBS): Weigh KH_2PO_4 11.58g, H_3PO_4 (85%) 10.9g, add water To 1000ml.

Mobile phase A: PBS 468g 26g mixed with acetonitrile, filtered and degassed

Mobile phase B: PBS 536g 338g mixed with acetonitrile, filtered and degassed

Methods of operation:

Flow rate 1ml / min; detection wavelength: 214nm; column temperature: 55 ° C

Determination:

The standard was diluted with water for injection to a different concentration of the solution, with the above-described operation of the high-performance liquid Methods for testing different concentrations of different standards obtained peak area, and then use Excel software Standard curve to give the formula to prepare the sample for quantification.

Content of the sample calculation: take samples above HPLC method of operation is detected, and the resulting The peak area is substituted into the formula for the calculation of the standard curve, you can get the content of the sample.

Related substances computing: the peak area of the total impurity content of the integrated area calculation.

Table 1: stability under different pH conditions of the sample

Results: Exenatide are easily degradable in pH4.5 or less than 5.5, and in 4.5, 5.5 when more stable, Both to pH4.5 is the best. The present invention is preferably disodium hydrogen phosphate - citrate buffer, because citric acid itself Has a bactericidal effect, the long-term storage of formulations having a certain effect, but also has the addition of citric acid for analgesic Use, can reduce the pH of the formulation due to the more acid in the injection brought pain.

Peptide drug injection compositions, suitable stabilizing agents for stabilizing peptide drug is extremely important The (Wang W, Martin-Moe S, Pan C et al. Stabilization of a polypeptide in non-aqueous solvents. Int J Pharm.2007 Sep 15) For the

purposes of the present invention, the inventors also studied a lot Different preparation materials on exenatide stability. Polypeptide formulations generally suitable for application materials have carbohydrates, Amino acids, surfactants, alcohols, metal chelating agent. The present invention is suitable for a number of selected body should With excipients were screened.

Suitable for a variety of sugars present invention may optionally monosaccharides, oligosaccharides and polysaccharides and phospholipids and nucleotide derivatives. Typical examples are as follows: trivalent and higher sugar alcohols, such as glycerol,, erythritol, arabitol, xylitol, Sorbitol and mannitol; acidic sugars such as glucuronic acid, iduronic acid, neuraminic acid, galactose Glucuronic acid, glucose acid, mannuronic acid, hyaluronic acid and its salts, chondroitin sulfate and its salts, as well as liver Su, inulin, chitin and derivatives thereof, dextrin, dextran average molecular weight of 5000-150000 and Alginate acid and its salts. These sugars can be added separately, it can also be used in combination.

Useful in the present invention are peptides, amino acids and derivatives can be selected from a group consisting of the following comes: Glycine, alanine, serine, aspartic acid, glutamic acid, threonine, tryptophan, lysine, hydroxyl Lai Histidine, arginine, cystine, cysteine, methionine, phenylalanine, leucine, iso Leucine and derivatives thereof. They can be added separately, it can also be used in combination.

Useful in the present invention is nonionic surfactants, e.g., sorbitan fatty acid esters, glycerin fatty acid Esters (such as sorbitan caprylate monoesters, sorbitan monolaurate alcohol and dehydration of sorbitol palmitate Monoester), polyglycerol fatty acid esters (such as glycerol mono- caprylate, glyceryl myristate single cream butter and glycerin stearin Fatty acid monoester), polyoxyethylene sorbitan fatty acid esters, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene Alkenyl glycerol fatty acid esters, polyoxyethylene glycol fatty acid esters, polyoxyethylene alkyl ethers, polyoxyethylene polyoxypropylene Alkyl ethers, polyoxyethylene phenyl ethers, polyoxyethylated hard castor oil, polyoxyethylated beeswax derivatives, polyoxyethylene Ethylene derivatives of lanolin or a polyoxyethylene fatty acid amide, a cationic surfactant is an alkyl sulfate (If an alkyl C10-C18 alkyl sulphates), polyvinyl alkyl ether sulfates, sulfosuccinate salts, Natural surfactants are: lecithin, glycerophospholipids, sphingomyelin, sucrose fatty acid esters and the like. Of course, this These surfactants may be used alone, in combination.

[20]

In order to study the different materials additives added stability conditions exenatide, made the following real Test, as follows: first, the preparation of different materials solution and then weighed exenatide, we add it to a different Materials dissolved in the solution as a solution formulation of exenatide about 10µg / 0.2ml, each group contains different excipients 20mM pH4.5 disodium hydrogen phosphate - citrate buffer, and both with NaOH or HCl pH adjusted to 4.5. Match After the system put in 40 ° C oven for accelerated tests, weekly sampling by HPLC, product degradation was observed situation Case, concrete results in the table below.

Table 2: Composition table accessories

Following is a different formulation stability results:

[1]

(1)Clarity of the sample

Table 3 shows the sample at 40 ° C when stored for 4 weeks, no turbidity phenomenon.

Table 3: Sample 4 Zhou Chengming detection result stored at 40 ° C conditions

(2)

RP-HPLC detector

The use of RP-HPLC method for detection of weekly sampling. Tables 4 and 5 shows the sample in 40 ° C accelerated conditions , Only the content of the sample with a peptide related substances mannitol and methionine contained no major changes, Related substances other samples have a larger increase, the peptide decreased significantly.

Table 4: samples stored under conditions of 40 ° C for 4 weeks, for each week the detection of related substances by RP-HPLC

Table 5: sample storage conditions at 40 ° C for 4 weeks, weekly detected by RP-HPLC peptide content

Based on the above results, the following conclusions: sugars (including glucose, sucrose, mannitol) It adds, exenatide can play a stabilizing role; surfactants can reduce the growth of related substances Plus; EDTA has no effect on the stability of the formulation; and amino acids glycine or methionine able to The stability of the work products, especially for the preparation of methionine can have the best protection, methionine In the formulation of antioxidants and isotonic plays the dual role of regulator can reduce the increase related substances, and can So exenatide peptide content in the formulation is stable, so the final preferred methionine as exenatide system Accessories agent. Taking into account the osmotic pressure injection formulation should be close to physiological osmotic pressure, so the election Optional 3% (W / V) concentrations of methionine as a preparation optimal dosage.

Through the above study, the inventors considered the following combinations of agents are desirable: 10-500µg / ml of Exenatide, preferably 30-150µg / ml, the optimal concentration of 50µg / ml; appropriate concentrations of methionine Acid, glycine, glucose, sucrose, or mannitol, preferably 1% to 6% concentration (w / v) methionine, and more Selected from 2-4% concentration (w / v) methionine, methionine concentration is most preferably 3%. The selected buffer may be Independently selected from disodium hydrogen phosphate - citric acid buffer, phosphate buffer, acetate buffer, sodium barbital buffer, Or a citrate buffer, at a concentration of 5-100mmol / L, preferably 10-30mmol / L, most preferably 20mmol / L; Buffer in the pH range 3.0 to 7.0, preferably 4.0 to 6.0, most preferably pH 4.5. Wherein, preferably the buffer Phosphate buffer, disodium hydrogen phosphate - citric acid buffer solution or acetic acid - sodium acetate buffer, most preferred are phosphoric acid Disodium hydrogen phosphate - citric acid buffer at a concentration of 5-100mmol / L, preferably 10-30mmol / L, most preferred concentrations Of 20mmol / L, pH range between 3.0 to 7.0 in the solution, preferably 4.0-6.0, most preferably pH 4.5.

As an alternative, disclosed in Example 1, a more appropriate prescription formulation of exenatide, which Exendin-4 concentration was 50µg / ml, the methionine concentration (w / v) was 3%, disodium hydrogen phosphate - citric Acid buffer concentration is 20mmol / L, pH of the solution is 4.5 to 0.2ml / support filling in 1ml of pre-irrigation Sealed syringe.

As required, the preparation of the above pharmaceutical formulation is freeze-dried powder.

The above-mentioned pharmaceutical preparations can be used alone metformin, sulfonylureas, or metformin and sulfonylurea Adjuvant therapy combined with drug treatment failed to achieve good control of type 2 diabetes, clinical use of Subcutaneous injection. A preferred clinical subcutaneously twice daily dosing regimen, each of exenatide 5-10µg The peptide.

According to exenatide injection preparation with the existing technical solution of the present invention is prepared (U.S. Patent US6902744 and US7115569) were compared under different conditions of stability. From the experimental results of Examples 2 Fruit can be seen in: pharmaceutical formulations at 4 ° C conditions of the present invention enables a high concentration and low concentration of exenatide Peptide content and related substances can remain stable; at 4 ° C conditions according to U.S. Patent (US6902744 and US7115569) has listed the development Pharmaceutical formulations allow high concentrations of exenatide in formulation Mediator Remained stable (ie no major changes peptide content and related substances), but it can not make low concentrations of exenatide Pharmaceutical formulations of the present invention at 25 ° C conditions; formulations remained stable, mainly peptide content greatly reduced Within six months to make a high concentration and low concentration of exenatide on

peptide content and related substances can remain stable Set; at 25 ° C, according to the US Patent (US6902744 and US7115569) has listed the development Pharmaceutical formulations can not remain stable in the Exenatide formulation, whether it is a high concentration or low concentration Exenatide, particularly low concentrations of Exenatide in a formulation is particularly evident change (peptide content greatly reduced, A large number of related substances increase). From this control experiments available, at room temperature in the pharmaceutical formulations of the present invention To maintain the stability of exenatide in the formulation is significantly better than in accordance with U.S. Patent (US6902744 and US7115569) has listed the development Pharmaceutical formulations, especially when using low concentrations of exenatide, the The more obvious advantages.

The present invention also studied the effects of different containers for preparation, see Example 3 results. research shows: Use 1ml disposable pre-filled syringe (pre-loaded needle) used in the present formulation storage container, not only consumer It can reduce pollution in the middle of the process; and compared with the conventional ampoules or vials packed in a very low drug Under concentration reflects more stable higher advantages.

Wherein the concentrations of the components of change in the basis of the pharmaceutical compositions of the present invention on or add other substances, but to improve Exenatide stability did not change significantly, it is still considered part of the present invention.

In order to further illustrate the present invention, there is provided the following examples, these examples are merely to further illustrate The present invention is not intended as a limitation.

BRIEF DESCRIPTION

1 exenatide peptide drug formulation preparation process routes a schematic diagram

detailed description

Examples of a

Exenatide prepared containing injectable pharmaceutical preparations

[50]

A certain amount of the drug exenatide, calculated according to the weight to be diluted prior exenatide 50µg / ml, final formulation volume (V1). Take the right amount of methionine added to the appropriate amount of sterile according to V1, said Dissolved in water, methionine content in the final preparation is 3% (W / V). Then add the appropriate amount of pH 4.5 The high concentration of disodium hydrogen phosphate - citrate buffer, so the buffer in the final formulation concentration of 20mmol / L. again We will say good exenatide drug into dissolved, 1mol / l HCL or 10% NaOH to adjust pH to 4.5. Finally, adding an appropriate amount of sterile water to dilute the formulation to achieve a final volume V1, using a 0.22 micron filter The formulation was sterile filtration membranes (Preparation process shown in Figure 1). In 0.2ml / support filling in 1ml prefilled Syringe.

Example Two

Comparative stability containing exenatide injection agent different prescriptions.

[1]

1)Pharmaceutical formulations 1 (refer to US patent (US6902744 and US7115569) has listed the development of AI Preparation products that plug peptide The pharmaceutical formulations)

Mannitol were weighed 40g and 2.2g of m-cresol was added to 700ml of sterile water dissolved, 150ml 0.2M acetic acid at pH 4.5 - sodium acetate buffer, said good 50mg exenatide drug was added into the solution Solution, with 1mol / l HCL or 10% NaOH to adjust the pH to 4.5. Finally, adding an appropriate amount of sterile water and diluted to make Final formulation

volume to 1000ml, exenatide final concentration of 50µg / ml. And filtered using 0.22 micron The formulation was sterile filtration membranes. In 0.2ml / support in 1ml of pre-filling the needle, the lot number 01 granted.

[0]

Formulated in the same manner as described above exenatide concentration of 200µg / 1000ml ml preparation and use 0.22 Micron filter formulation was sterile filtered. In 0.2ml / support in 1ml of pre-filling the needle, the batch No. 02 batches.

[2]

2)2 pharmaceutical formulations (pharmaceutical formulations of the present invention)

Weigh 30g methionine was added to 700ml of sterile water were dissolved, was added to 100ml pH 4.5 0.2M Disodium hydrogen phosphate - citrate buffer, said good 50mg drug exenatide put dissolved, 1mol / l HCL or 10% NaOH to adjust the pH to 4.5. Finally, adding an appropriate amount of sterile water to dilute the formulation of the final volume To 1000ml, exenatide final concentration of 50µg / ml. And 0.22 micron filter using the formulation Sterile filtered. In 0.2ml / support in 1ml of pre-filling the needle, the lot number 03 granted.

[0]

Formulated in the same manner as described above exenatide concentration of 200µg / 1000ml ml preparation and use 0.22 Micron filter formulation was sterile filtered. In 0.2ml / support in 1ml of pre-filling the needle, the batch No. 04 batches.

[3]

3)Two kinds of stability comparing different formulations of prescription

[3]

The four batches of these different prescription formulations stored at 25 ° C and 4 ° C environment: Place 6 at 25 ° C environment Months, 0,1,2,3,6 sampling for testing by RP-HPLC; for 18 months at 4 ° C environment, 0, 3Sampling for testing by RP-HPLC 6,9,12,18 months.

Table 14: two kinds of prescription formulations stored for six months at 25 ° C conditions, RP-HPLC test results

Table 15: two kinds of prescription formulation stored for 18 months at 4 ° C conditions, RP-HPLC test results

Examples from the experimental results can be seen in 2: Formulation prescription at 4 ° C conditions of the present invention enables a high concentration And low concentrations of exenatide on peptide content and related substances can remain stable; at 4 ° C conditions according to the United States Patent (US6902744 and US7115569) has listed the development Preparation prescription allows a high concentration Exenatide remained stable in the formulation (ie, peptide content and related substances no major changes), but it can not So that low concentrations of exenatide remained stable in the formulation, primarily peptide content greatly reduced; at 25 ° C Article Member under pharmaceutical formulations of the present invention enables a high concentration and low concentration within six months exenatide peptide content The related substances can remain stable; at 25 ° C, according to the US Patent (US6902744 and US7115569) has listed the development Pharmaceutical formulations of exenatide can not remain stable in the formulation Set, whether high or low density concentrations of exenatide in which low concentrations of exenatide change in the formulation Particularly evident (peptide content greatly reduced, a large number of related substances increase). From this control experiments available, Pharmaceutical formulations of the present invention at room temperature to maintain the stability of exenatide in the formulation is significantly better than According to the US Patent (US6902744 and US7115569) has listed the development Pharmaceutical formulations, in particular Do not use low concentrations of exenatide, the more obvious advantages.

Three examples

Screening experiments exenatide injection storage containers

Exenatide injection with 0.2ml / support were filled in 1ml preloaded needles, vials and ampoules , And were placed at -20 ° C, to inspect conditions at 4 ° C, for two weeks, sampling once a week. By Rong Pair exenatide injection sorption container of liquid usage of these two indicators to conduct investigations.

[1]

1、 Container injection of exenatide adsorption: detection by RP-HPLC to give the peptide content, To calculate the adsorption rate of container exenatide injection.

[2]

2、 Container for liquid medicine usage: exenatide injection from each of the different containers of twenty, the first sub Nickname their total weight (W1), the liquid after the play, and then were referred to their total weight (W2), medication can The total solution weight (W3 = W1-W2), 20 × 0.2ml exenatide injection weight W4, the utilization = (W3 / W4) × 100%.

Table 10: exenatide injection assay results in 1ml of pre needle

Table 11: exenatide injection in 1ml vials of assay results

Table 12: exenatide injection in 1ml ampoules assay results

Table 13: Three different containers for exenatide injection usage situation

From the above results can be obtained under the conditions of -20 ° C, exenatide filling in the three different vessels in Three kinds of container adsorption effect of the drug on the small difference, but at 4 ° C conditions of the present invention is used in a pre-needle 1ml Another relative adsorption of injection exenatide significantly reduced both containers; containers for use exenatide injection Rate this product is particularly important, since the smaller the amount of the volume of the product, a small amount of liquid in the injection process Losses may total amount of liquid will account for a large proportion of which will affect the efficacy of treatment, from Table 13 The experimental results can be obtained with a pre-needle can reduce the liquid remaining in the container, which can reduce the liquid in the injection Shot during a loss, so that liquid can be fully utilized. Adsorption experiments with liquid from the container usage situation Situation, the present invention employs the best choice for pre pin as the container is in line with the characteristics of the product.

Four examples

Long-term stability of the injectable formulation of exenatide

Prescription: 50µg / ml + 3% Methionine + 20mmol / L disodium hydrogen phosphate - citric acid buffer (pH 4.5) prepared three batches of formulation Example of a method, each batch is divided into two parts: one is placed at a temperature of 25 ° C, Relative humidity 60% ± 10% under accelerated testing conditions, respectively, 0, 1, 2, 3, June sample testing; Another place at a temperature of 4 ° C constant temperature environment of long-term tests, respectively at 0, 3, 6, 9, 12, 18 months sampling Testing.

Table 8: exenatide injection stability of the recording (storage conditions: 25 ° C)

Table 9: exenatide injection stability of the recording (storage conditions: 4 ° C)

From the above results can be seen, exenatide injection in three batches of 25 ° C under accelerated test conditions 6 Within months of the indexes are within the acceptable range, long-term study of the indexes were 18 months together Within a range of cells.



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CLAIMS CN101444618

[1]

1. The pharmaceutical preparation containing exendin peptide, wherein: said pharmaceutical formulation comprising exenatide Peptide formulation can be maintained in an aqueous solution pH of 3.0-7.0 and a buffer to enhance exenatide stable Of materials, said materials can be optionally selected from glucose, sucrose, methionine, mannitol or a glycine One or several.

[2]

2. The pharmaceutical formulation according to claim 1, characterized in that: said buffer optionally phosphorus from Dibasic acid - citric acid buffer, phosphate buffer, acetate buffer, citrate buffer or sodium pentobarbital Buffer concentration 5-100mmol / L, pH range 3.0 to 7.0.

[3]

3. The pharmaceutical formulation according to claim 2, characterized in that: said buffer is phosphate dibasic Sodium - citrate buffer at a concentration of 5-100mmol / L, pH range of 4.0-6.0.

[4]

4. The pharmaceutical formulation according to claim 1, wherein: said stability enhancement exenatide Excipients of methionine, the concentration (weight / volume of solution, w / v) of 1% to 6%.

[5]

5. The pharmaceutical formulation according to claim 4, wherein: said stability enhancement exenatide Excipients of methionine, the concentration (weight / volume of solution, w / v) was 3%.

[6]

6. The pharmaceutical formulation according to claim 1, wherein: Exenatide in a liquid formulation At a concentration of 10-500µg / ml.

[7]

7. The pharmaceutical formulation according to claim 1, characterized in that: in the liquid formulation of Exenatide At a concentration of 50µg / ml, methionine at a concentration (weight / volume of solution, w / v) was 3%, disodium hydrogen phosphate - Citrate buffer concentration of 20mmol / L, pH of the solution was 4.5.

[8]

8. The pharmaceutical formulation according to any one of claims 1-7, characterized in that: said pharmaceutical preparation Storage container is pre-filled syringes, vials or ampoules.

[9]

9 、 The pharmaceutical formulation according to one any one of claims 1-7, characterized in that: the pharmaceutical preparations may Prepared as a freeze-dried powder.

[10]

10. Exenatide to claim preparing a pharmaceutical formulation according to any one of 1-7, the medicament Formulations for the treatment of type 2 diabetes.