

Sealed single-dose container of levothyroxine aqueous solution suitable for oral administration

Description of the invention

- 5 The present invention relates to blow-fill-seal (BFS) sealed single-dose containers comprising a pharmaceutical composition of an aqueous solution for use in oral administration, which composition comprises levothyroxine or liothyronine or a pharmaceutically acceptable salt thereof, preferably levothyroxine sodium, water and one or more co-solvents and is alcohol-free, exhibits a pH from 8,1 to 8,7, an
10 average density from 1,18 to 1,23 grams per milliliter (g/mL), and viscosity from 20 to 60 cps.

The thyroid gland is one of the most important endocrine glands of the human body as it regulates various metabolic functions. The thyroid gland secretes the hormones liothyronine (T3) and levothyroxine (T4), which are vital for the metabolism and
15 normal physical and mental development of humans under the control of the pituitary hormone thyrotropin (TSH). Especially in the fetus and the newborn, thyroid hormones have a decisive role in the normal development of the central nervous system. Underactive thyroid is referred as hypothyroidism. In hypothyroidism there is a deficiency of T3 and T4 and an increase in TSH levels. The incidence of congenital
20 hypothyroidism, called congenital hypothyroidism, is up to 1:4000 newborns, with a higher incidence in girls, where it occurs in a 2:1 ratio compared to boys. Untimely detection of congenital hypothyroidism can lead to irreversible damage to the newborn's nervous system and permanent mental retardation. In childhood, the effects of hypofunction of the thyroid gland (e.g. due to undertreatment of the
25 patient) can lead to disorders of psychomotor development, disorders of the child's growth and performance, anemia, etc. But even in adults increasingly disorders in the functioning of the thyroid gland are more often encountered, which have a direct consequence both in the daily life of the person (fatigue, weakness, sleepiness, fluctuations in body weight, etc.) and in the long term since they can cause an
30 increase in cardiovascular morbidity and mortality.

Modern treatment of hypothyroidism includes the oral administration of synthetic levothyroxine, usually its sodium salt, in tablet form. The effective dose is determined after conducting regular clinical examinations and is equivalent to about 1,7 µg/kg per day, which for an average person corresponds to about 80–150 µg per day. The tablet dissolves in the acidic pH of the gastric environment and levothyroxine is transported to the intestine, where it is absorbed by the intestinal epithelium in the first three hours after administration, at a rate of approximately 70%, either in the upper part of the jejunum or in the lower part of the small intestine, in the ileum [Hays MT. Localization of human thyroxine absorption. *Thyroid* 1991, 1, 241–248]. Intestinal absorption disorders in malabsorption syndromes (e.g. celiac disease), food rich in plant fibers, as well as the co-administration of other pharmaceuticals (e.g. iron, calcium) may reduce the absorption of levothyroxine, while fasting increases it. For these reasons, it is recommended that levothyroxine to be taken on an empty stomach and at different times than other medications.

Replacement therapy for congenital hypothyroidism in infants, toddlers and young children is carried out with levothyroxine tablets, which are dissolved in water and given either by syringe (infants) or with a spoon to swallow (older ages). However, the current consensus guidelines for congenital hypothyroidism prohibit the creation of multiple-use suspensions from the tablets, due to the sensitivity of levothyroxine to moisture and light and its tendency to decompose to other compounds such as liothyronine (T3), 2- (4-(4-hydroxy-3,5-diiodophenoxy)-3,5-diiodophenyl)acetic acid (TETRAC), (4-(4-hydroxy-3,5-diiodophenoxy)-3,5-diiodobenzoic acid (TETRAFA) and others.

Therefore, it is considered necessary to develop stable liquid preparations of levothyroxine whose use will, on the one hand, address the practical and technical problems arising from the need for daily dissolution of the tablets and, on the other hand, will facilitate administration to newborns, infants and children. Also, it is necessary to ensure the accuracy of the administered dose, while at early young ages there is always the concern that the tablet form may not be dissolved sufficiently and isomerically in water and therefore the appropriate dose may not always be taken.

Various solutions of levothyroxine have been reported in the state of the art.

Document WO2013072304 relates to single-dose compositions of thyroid hormones in alcoholic-aqueous solutions. These compositions are stored in low density polyethylene containers, which are then secondarily sealed in a laminated envelope consisting of polyethylene, aluminum and polyethylene terephthalate or alternatively
5 in laminated containers. The specific containers prevent the evaporation of the ethanol and, by extension, the alteration of the composition of the solution. However, these formulations are not indicated for pediatric patients due to the presence of ethanol.

Document WO2018073209 relates to single-dose compositions of thyroid hormones
10 in glycerol-water solutions, which are stored in low density polyethylene containers which are then secondarily sealed in a laminate envelope consisting of polyethylene, aluminum and polyethylene terephthalate to ensure its stability solution.

Document GR20100100508 refers to solutions of levothyroxine in the combination of ethanol, propylene glycol and water. These solutions can be formed into drops and
15 remain stable for three months under normal storage conditions, i.e. at a temperature of 25°C and a humidity of 60%. These compositions also comprise 15-30% ethanol and are contraindicated for use in pediatric and geriatric patients.

Document WO2016137969 refers to solutions of levothyroxine in glycerol and water, wherein the percentage of glycerol is at least 70%. In addition, these solutions
20 comprise, as an antioxidant agent, ethylenediaminetetraacetic acid (EDTA) at a rate of up to 1,5% in order to achieve the required stability of the solution.

Document EP2683361 refers to a preparation method of levothyroxine solutions in glycerol and water which have a final pH between 5-6 and which owe their stability to the presence of preservatives including the sodium salt of methyl p-
25 hydroxybenzoate.

All the above aforementioned compositions of levothyroxine solutions either use solvents incompatible for use in pediatric and geriatric populations (e.g., high concentrations of ethanol), or use preservatives (e.g. methyl p-hydroxybenzoate) and antioxidants (e.g. ethylenediaminetetraacetic acid) substances, either not single-
30 dose, or not having a pH from 8,1 to 8,7, an average density from 1,18 to 1,23 grams per milliliter (g/mL), and viscosity from 20 to 60 cps, so as to achieve their long-term maintenance.

Despite of the achievements already mentioned in the state of the art, due to the increased requirements in quality and safety, there is a continuous need to further improve the stability and accuracy of the dose of levothyroxine aqueous solution.

However, blow-fill-seal (BFS) sealed single-dose containers comprising a pharmaceutical composition of an aqueous solution for use in oral administration, which composition comprises levothyroxine or liothyronine or a pharmaceutically acceptable salt thereof, preferably levothyroxine sodium, water and one or more co-solvents and is alcohol-free, exhibits a pH from 8,1 to 8,7, an average density from 1,18 to 1,23 grams per milliliter (g/mL), and viscosity from 20 to 60 cps have not been reported in the prior art yet.

This new proposed combination of container and composition with these specific characteristics as presented in the present invention exhibits all the advantages of the state of the art and even more with unexpectedly improved stability over time.

More specifically, the present invention is defined by the following:

Definition 1. Blow-fill-seal (BFS) sealed single-dose container comprising a pharmaceutical composition of an aqueous solution for use in oral administration, which composition comprises levothyroxine or liothyronine or a pharmaceutically acceptable salt thereof, preferably levothyroxine sodium, water and one or more co-solvents and is alcohol-free, exhibits a pH from 8,1 to 8,7, an average density from 1,18 to 1,23 grams per milliliter (g/mL), and viscosity from 20 to 60 cps.

Definition 2. Sealed single-dose container according to definition 1, wherein the concentration of levothyroxine or liothyronine or salts thereof ranges from 0,0005% to 0,2% weight by volume (w/v) of the final solution.

Definition 3. Sealed single-dose container according to any of the definitions 1 to 2, which is made of low-density polyethylene and placed in aluminum sachets.

Definition 4. Sealed single-dose container according to any of the definitions 1 to 3, wherein the co-solvents are preferably selected from polyols, such as alkanetriols,

alkanediols and polyethylene glycol, acetone, benzyl benzoate, phthalates, such as dibutyl phthalate, diethyl phthalate, dimethyl phthalate, dimethyl sulfoxide, dimethylacetamide, glycofurool, isopropyl myristate, isopropyl palmitate, propylene carbonate, pyrrolidine, glycerin triacetate, triethyl citrate, trilein, or a combination of
5 two or more thereof, preferably the co-solvent comprises glycerin and more preferably the co-solvent is only glycerin.

Definition 5. Sealed single-dose container according to any of the definitions 1 to 4, wherein the percentage of glycerin in the composition ranges from 85% to 95%
10 weight by volume (w/v) of the total amount of the solution.

Definition 6. Sealed single-dose container according to any of the definitions 1 to 5, wherein the composition is free of preservatives, for example methyl p-hydroxybenzoate and/or propyl p-hydroxybenzoate, and/or antioxidants, for example
15 ethylenediaminetetraacetic acid.

Definition 7. Sealed single-dose container according to any of the definitions 1 to 6, wherein the composition comprises pH buffers, which pH buffers are preferably selected from metal hydroxides and/or citric acid and/or salts thereof.
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Definition 8. Sealed single-dose container according to any of the definitions 1 to 7, wherein the composition comprises a pharmaceutically acceptable flavoring agent preferably selected from strawberry, banana, apricot, cherry, orange, lemon, caramel and/or coffee.
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Definition 9. Sealed single-dose container according to any of the definitions 1 to 8, for use in the management, treatment or prevention of hypothyroidism in neonatal, pediatric, adult and geriatric patients, of goitre, of nodular thyroid disease, of thyroid cancer, of subclinical hypothyroidism and of myxoedematous coma.
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It was surprisingly found that the blow-fill-seal (BFS) sealed single-dose containers comprising a pharmaceutical composition of an aqueous solution for use in oral administration, which composition comprises levothyroxine or liothyronine or a pharmaceutically acceptable salt thereof, preferably levothyroxine sodium, water and one or more co-solvents and is alcohol-free, exhibits increased stability over time, especially when it exhibits a pH from 8,1 to 8,7, an average density from 1,18 to 1,23 grams per milliliter (g/mL), and viscosity from 20 to 60 cps and more specifically at least one year longer shelf life than aqueous solutions of levothyroxine in other types of containers e.g. multi-dose.

In addition to stability, it was surprisingly found that while it is a single dose, it has the advantage of the precision of the dose that the patient receives.

Moreover, it was surprisingly found that due to the fact that this solution does not comprise alcohol, improves patient tolerance, as it does not cause the slightest irritation or toxicity even in pediatric patients.

Furthermore, it was surprisingly found that the more is restricted the scope of the claims, the more intense are the effects and the advantages of the present invention.

The compositions of the present invention can be prepared by methods already known in the state of art.

The present invention is further described by the following indicative, but non-limiting example.

Example 1: In a preferred embodiment the composition of the present invention comprises the following per mL

Levothyroxine Sodium (anhydrous)	0,100 mg (corresponds to 0,113 mg Levothyroxine Sodium)
Glycerin 99,5% w/w	900 mg
NaOH (1M)	Q.s. pH 8,5

Trisodium citrate (dihydrate)	5,882 mg
Purified Water	Q.s. 1 mL

The above composition exhibits an average density from 1,18 to 1,23 grams per milliliter (g/mL) and a viscosity from 20 to 60 cps.

The composition of the present examples 1 exhibits all the advantages of the present invention mentioned above.

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Claims

1. Blow-fill-seal (BFS) sealed single-dose container comprising a pharmaceutical composition of an aqueous solution for use in oral administration, which composition comprises levothyroxine or liothyronine or a pharmaceutically acceptable salt thereof,
5 preferably levothyroxine sodium, water and one or more co-solvents and is alcohol-free, exhibits a pH from 8,1 to 8,7, an average density from 1,18 to 1,23 grams per milliliter (g/mL), and viscosity from 20 to 60 cps.
2. Sealed single-dose container according to claim 1, wherein the concentration of
10 levothyroxine or liothyronine or salts thereof ranges from 0,0005% to 0,2% weight by volume (w/v) of the final solution.
3. Sealed single-dose container according to any of the claims 1 to 2, which is made of low-density polyethylene and placed in aluminum sachets.
15
4. Sealed single-dose container according to any of the claims 1 to 3, wherein the co-solvents are preferably selected from polyols, such as alkanetriols, alkanediols and polyethylene glycol, acetone, benzyl benzoate, phthalates, such as dibutyl phthalate, diethyl phthalate, dimethyl phthalate, dimethyl sulfoxide, dimethylacetamide,
20 glycofurol, isopropyl myristate, isopropyl palmitate, propylene carbonate, pyrrolidine, glycerin triacetate, triethyl citrate, trilein, or a combination of two or more thereof, preferably the co-solvent comprises glycerin and more preferably the co-solvent is only glycerin.
- 25 5. Sealed single-dose container according to any of the claims 1 to 4, wherein the percentage of glycerin in the composition ranges from 85% to 95% weight by volume (w/v) of the total amount of the solution.
6. Sealed single-dose container according to any of the claims 1 to 5, wherein the
30 composition is free of preservatives, for example methyl p-hydroxybenzoate and/or

propyl p-hydroxybenzoate, and/or antioxidants, for example ethylenediaminetetraacetic acid.

7. Sealed single-dose container according to any of the claims 1 to 6, wherein the
5 composition comprises pH buffers, which pH buffers are preferably selected from metal hydroxides and/or citric acid and/or salts thereof.

8. Sealed single-dose container according to any of the claims 1 to 7, wherein the
composition comprises a pharmaceutically acceptable flavoring agent preferably
10 selected from strawberry, banana, apricot, cherry, orange, lemon, caramel and/or coffee.

9. Sealed single-dose container according to any of the claims 1 to 8, for use in the
management, treatment or prevention of hypothyroidism in neonatal, pediatric, adult
15 and geriatric patients, of goitre, of nodular thyroid disease, of thyroid cancer, of subclinical hypothyroidism and of myxoedematous coma.