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(71) Applicant: **SPECTRIX THERAPEUTICS, LLC** [US/US]; 1256 Main Street, Suite 249, Southlake, TX 76092 (US).

(72) Inventor: **TENGLER, Mark**; 1256 Main Street, Suite 249, Southlake, TX 76092 (US).

(74) Agent: **CHALKER, Daniel, J.** et al.; CHALKER FLORES, LLP, 14951 North Dallas Parkway, Suite 400, Dallas, TX 75254 (US).

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(54) Title: COMPOSITIONS AND METHODS OF PROVIDING THYROID HORMONE OF ANALOGS THEREOF

(57) Abstract: The present invention includes a pharmaceutical composition and method of making and using comprising one or more thyroid hormones or analogs thereof, wherein a first portion of thyroid hormone is formulated for modified release and a second portion of the one or more thyroid hormones is formulated for modified release, wherein the combination of the first and second portion are provided in an amount effective to treat hypothyroidism.

COMPOSITIONS AND METHODS OF PROVIDING THYROID HORMONE OR ANALOGS THEREOF

TECHNICAL FIELD OF THE INVENTION

The present invention relates in general to the field of compositions and methods for the delivery of thyroid hormones or analogs thereof, and more particularly, to novel formulations for the delivery of thyroid hormones.

BACKGROUND OF THE INVENTION

Without limiting the scope of the invention, its background is described in connection with treatments for hypothyroidism.

United States Patent No. 9,220,788, issued to Davis, et al., is entitled "Nanoparticle and polymer formulations for thyroid hormone analogs, antagonists, and formulations and uses thereof." Briefly, the invention is said to include methods of treating subjects having conditions related to angiogenesis including administering an effective amount of a polymeric nanoparticle form of thyroid hormone agonist, partial agonist or an antagonist thereof, and to promote or inhibit angiogenesis in the subject.

United States Patent No. 7,723,390, issued to Garavani, is entitled, "Pharmaceutical formulations for thyroid hormones". Briefly, the invention is said to provide for pharmaceutical formulations based on thyroid hormones enabling a safe and stable oral administration in the framework of the strict therapeutic index prescribed in case of thyroid disorders.

United States Patent Publication No. 20070099841, filed by Moncrief, et al., is entitled "Prodrugs of T3 and T4 with enhanced bioavailability". These applicants are said to teach compositions of amino acid and peptide conjugates comprising T3 and/or T4. The T3 or T4 is covalently attached to at least one amino acid via the N-terminus, the C-terminus, a side chain of the peptide carrier, and/or interspersed within the peptide chain. Also discussed are methods for protecting and administering active agents and methods for treating thyroid disorders.

SUMMARY OF THE INVENTION

In one embodiment, the present invention includes a pharmaceutical composition comprising one or more thyroid hormones or analogs thereof, wherein a first portion of thyroid hormone is formulated for modified release and a second portion of the one or more thyroid hormones is

formulated for modified release, wherein the combination of the first and second portion are provided in an amount effective to treat hypothyroidism. In one aspect, the first portion is a T3 thyroid hormone provided at 1-50% modified release, and the second portion is a T4 thyroid hormone provided at 50-99% modified release. In another aspect, the first portion is a T4 thyroid hormone provided at 50-99% modified release, and the second portion is a T3 thyroid hormone provided at 1-50% modified release. In another aspect, the first portion is a T3 and T4 thyroid hormone provided at 10-90% modified release, and the second portion is a T3 and T4 thyroid hormone provided at 90-10% modified release. In another aspect, at least one of the thyroid hormone(s) are bound to an ion resin, the one or more thyroid hormones are selected from at least one of T4, T3, T4 or T3 N-Methyl, T4 or T3 N-Ethyl, T4 or T3 N-Triphenyl, T4 or T3 N-Propyl, T4 or T3 N-Isopropyl, T4 or T3-N-Tertiary butyl, GC-1, DIPTA, Tetrac, or Triac, and optionally the modified release thyroid hormone is T3. In another aspect, the composition further comprises one or more pharmaceutically acceptable carriers, one or more additional biologically active substances, and wherein the composition is adapted for the treatment of hypothyroidism. In another aspect, at least one of the thyroid hormones is T4 or T3, and the ion exchange resin prevents polymorphism in the crystalline structure of the bound hormone. In another aspect, the binding of thyroid hormone to resin provides a geometric dilution to aid in the ease of manufacturing and increase consistency in dosing. In another aspect, the composition is a liquid suspension, chewable composition, orally disintegrating tablet, sublingual, a modified release orally disintegrating tablet, or a swallowed tablet composition. In another aspect, the one or more thyroid hormones are T4 and T3, and are provided a ratio of T4:T3 is from 1:1 to 20:1. In another aspect, the ion-exchange resin particles are an acidic cation exchange resin, a basic anion exchange resin, and they are optionally coated with a triggered-release coating that is triggered by a pH change or a non-pH dependent controlled release coating. In another aspect, the composition is coated and the coating is selected from at least one of cellulose acetate phthalate, cellulose acetate trimellitate, hydroxypropyl methylcellulose phthalate, polyvinyl acetate phthalate, carboxymethylethylcellulose, co-polymerized methacrylic acid/methacrylic acid methyl esters, co-polymerized methacrylic acid/ acrylic acid ethyl esters, or mixtures thereof. In another aspect, the amount of the one or more thyroid hormones is from 0.013 to 0.30 mg equivalent of levothyroxine sodium per dose. In another aspect, an amount greater than 40%, 50%, 60%, 70%, or 80% of the first thyroid hormone is released within the first 45 minutes after the product is introduced into an in vitro dissolution assay, wherein the conditions of the dissolution assay are an initial dissolution medium of 0.1 N HCl, and after 2 hours, the medium

is adjusted to a pH of about 6.8, and the dissolution assay is performed using a USP Apparatus 2. In another aspect, the composition consists essentially of at least two thyroid hormones or analogs thereof, wherein a first thyroid hormone or analogs thereof is formulated for immediate release and wherein a second thyroid hormone or analogs thereof is bound to ion resin particles, wherein the drug-resin particles may be uncoated or coated with an immediate release coating, wherein at least 80% of the drug is released within one hour, and wherein the one or more thyroid hormones are selected from at least one of T4, T3, T4 or T3 N-Methyl, T4 or T3 N-Ethyl, T4 or T3 N-Triphenyl, T4 or T3 N-Propyl, T4 or T3 N-Isopropyl, T4 or T3-N-Tertiary butyl, GC-1, DIPTA, Tetrac, or Triac.

In another embodiment, the present invention includes a pharmaceutical composition comprising thyroid hormone(s) complexed with ion-exchange resin particles to form drug resin particles, wherein the composition comprises a first plurality of immediate release drug-resin particles and a second plurality of drug-resin particles that are coated for modified release, wherein the composition has an *in vivo* fasted serum profile with a first and second peak wherein the first peak occurs before 3 hours after ingestion of the composition and the second peak occurs after 3 hours after ingestion.

In another embodiment, the present invention includes a method of making a pharmaceutical composition comprising: attaching a first portion of a first thyroid hormone or analogs thereof to ion-exchange resin particles to form drug-resin particles; attaching a second portion of a second thyroid hormone or analogs thereof to ion-exchange resin particles to form drug-resin particles; and wherein at least 10-90% or more by weight of the first portion of thyroid hormone(s) is formulated for modified release, and at least 90-10% or more by weight of the second portion of thyroid hormone(s) is formulated for modified release, wherein the first and second portions are provided in an amount effective to treat hypothyroidism. In one aspect, the one or more thyroid hormones are selected from T4, T3, T4 or T3 N-Methyl, T4 or T3 N-Ethyl, T4 or T3 N-Triphenyl, T4 or T3 N-Propyl, T4 or T3 N-Isopropyl, T4 or T3-N-Tertiary butyl, GC-1, DIPTA, Tetrac and Triac, and optionally the modified release thyroid hormone is T3. In another aspect, the composition further comprises one or more pharmaceutically acceptable carriers, one or more additional biologically active substances, and wherein the composition is adapted for the treatment of hypothyroidism. In another aspect, at least one of the thyroid hormones is T4 or T3, and ion exchange resin prevents polymorphism in the crystalline structure of the bound hormone. In another aspect, the method further comprises binding of thyroid hormone to resin provides a geometric dilution to aid in the ease of manufacturing and

increase consistency in dosing. In another aspect, the method further comprises formulating the composition as a liquid suspension, a chewable composition, an orally disintegrating tablet, a sublingual tablet, a modified release orally disintegrating tablet, or a swallowed tablet. In another aspect, the one or more thyroid hormones are T4 and T3, and are provided a ratio of T4:T3 is from 1:1 to 20:1. In another aspect, the resin particles are ion-exchange resin particles selected from at least one of an acidic cation exchange resin or a basic anion exchange resin, and the resin particles are optionally coated with a triggered-release coating that is triggered by a pH change or a non-pH dependent controlled release coating. In another aspect, the method further comprises coating the composition with a coating selected at least one of cellulose acetate phthalate, cellulose acetate trimellitate, hydroxypropyl methylcellulose phthalate, polyvinyl acetate phthalate, carboxymethylethylcellulose, co-polymerized methacrylic acid/methacrylic acid methyl esters, co-polymerized methacrylic acid/ acrylic acid ethyl esters, or mixtures thereof. In another aspect, the amount of the one or more thyroid hormones is from 0.013 to 0.30 mg equivalent of levothyroxine sodium per dose. In another aspect, an amount greater than 40%, 50%, 60%, 70%, or 80% of the first thyroid hormone is released within the first 45 minutes after the product is introduced into an in vitro dissolution assay, wherein the conditions of the dissolution assay are an initial dissolution medium of 0.1 N HCl, and after 2 hours, the medium is adjusted to a pH of about 6.8, and the dissolution assay is performed using a USP Apparatus 2. In another aspect, a second portion of thyroid hormone provided for modified release comprises greater than 10% by weight. In another aspect, the method further comprises attaching thyroid hormone(s) or analogs thereof to ion-exchange resin particles to form drug-resin particles, wherein there is at least 30% or more weight gain in the drug-resin particles.

In yet another embodiment, the present invention includes a method of evaluating a formulation believed to be useful in treating hypothyroidism, the method comprising: (a) measuring the blood levels of one or more thyroid hormones from a first set of subjects suspected of having hypothyroidism; (b) administering the formulation to a first subset of the patients, and a placebo to a second subset of the patients, wherein the formulation comprises a first portion of thyroid hormone is formulated for modified release and a second portion of the one or more thyroid hormones is formulated for modified release, wherein the combination of the first and second portion are provided in an amount effective to treat hypothyroidism; (c) repeating step (a) after the administration of the formulation or the placebo; and (d) determining if the formulation reduces the number of hypothyroidism that is statistically significant as compared to any

reduction occurring in the second subset of patients, wherein a statistically significant reduction indicates that the formulation is useful in treating hypothyroidism.

DETAILED DESCRIPTION OF THE INVENTION

While the making and using of various embodiments of the present invention are discussed in detail below, it should be appreciated that the present invention provides many applicable inventive concepts that can be embodied in a wide variety of specific contexts. The specific embodiments discussed herein are merely illustrative of specific ways to make and use the invention and do not delimit the scope of the invention.

To facilitate the understanding of this invention, a number of terms are defined below. Terms defined herein have meanings as commonly understood by a person of ordinary skill in the areas relevant to the present invention. Terms such as "a", "an" and "the" are not intended to refer to only a singular entity, but include the general class of which a specific example may be used for illustration. The terminology herein is used to describe specific embodiments of the invention, but their usage does not delimit the invention, except as outlined in the claims.

As used herein, the term "pharmaceutically effective amount" refers to that amount of an agent effective to produce the intended effect of reducing, and/or preventing hypothyroidism. Hypothyroidism may be caused by decreased production of thyroid hormones. Such factors include loss of thyroid tissue due to disease or surgery.

Pharmaceutical composition refers to a composition suitable for pharmaceutical use in an animal or animal cell line. The animal may be a mammal, such as a human. A pharmaceutical composition of the invention includes a pharmaceutically effective amount of one or more thyroid hormones or analogs thereof, and optionally a pharmaceutically acceptable resin.

As used herein, the term "flavorant" is intended to mean a compound used to impart a pleasant flavor and often odor to a pharmaceutical preparation. In addition to the natural flavorants, many synthetic flavorants are also used. Such compounds include, by way of example and without limitation, anise oil, cinnamon oil, cocoa, menthol, orange oil, peppermint oil and vanillin and the like.

As used herein, the term "sweetening agent" is intended to mean a compound used to impart sweetness to a preparation. Such compounds include, by way of example and without limitation, aspartame, dextrose, glycerin, mannitol, saccharin sodium, sorbitol and sucrose and the like.

As used herein, the term "tablet antiadherents" is intended to mean agents which prevent the sticking of table formulation ingredients to punches and dies in a tableting machine during production. Such compounds include, by way of example and without limitation, magnesium stearate, talc, and the like.

As used herein, the term "tablet binders" is intended to mean substances used to cause adhesion of powder particles in table granulations. Such compounds include, by way of example and without limitation, acacia, alginic acid, carboxymethyl cellulose, sodium, compressible sugar ethylcellulose, gelatin, liquid glucose, methylcellulose, povidone and pregelatinized starch and the like.

As used herein, the term "tablet and capsule diluent" is intended to mean inert substances used as fillers to create the desired bulk, flow properties, and compression characteristics in the preparation of tablets and capsules. Such compounds include, by way of example and without limitation, dibasic calcium phosphate, kaolin, lactose, mannitol, microcrystalline cellulose, powdered cellulose, precipitated calcium carbonate, sorbitol, and starch and the like.

As used herein, the term "tablet direct compression excipient" is intended to mean a compound used in direct compression tablet formulations. Such compounds include, by way of example and without limitation, dibasic calcium phosphate and the like.

As used herein, the term "tablet disintegrant" is intended to mean a compound used in solid dosage forms to promote the disruption of the solid mass into smaller particles that are more readily dispersed or dissolved. Such compounds include, by way of example and without limitation, alginic acid, carboxymethylcellulose, calcium, microcrystalline cellulose, polacrilin potassium, sodium alginate, sodium starch glycolate, and starch and the like.

As used herein, the term "tablet glidant" is intended to mean agents used in tablet and capsule formulations to reduce friction during tablet compression. Such compounds include, by way of example and without limitation, colloidal silica, cornstarch, talc, and the like.

As used herein, the term "tablet lubricant" is intended to mean substances used in tablet formulations to reduce friction during tablet compression. Such compounds include, by way of example and without limitation, calcium stearate, magnesium stearate, mineral oil, stearic acid, zinc stearate, and the like.

As used herein, the term "tablet/capsule opaquant" is intended to mean a compound used to render a capsule or a tablet coating opaque. An opaquant may be used alone or in combination

with a colorant. Such compounds include, by way of example and without limitation, titanium dioxide and the like.

As used herein, the term "tablet polishing agent" is intended to mean a compound used to impart an attractive sheen to coated tablets. Such compounds include, by way of example and without limitation, carnauba wax, white wax, and the like.

It should be understood, that compounds used in the art of pharmaceutical formulation generally serve a variety of functions or purposes. Thus, if a compound named herein is mentioned only once or is used to define more than one term herein, its purpose or function should not be construed as being limited solely to that (those) named purpose(s) or function(s).

For oral therapeutic administration, the particles containing the active compound(s) may be incorporated with excipients and used in the form of ingestible tablets, buccal tables, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. Such compositions and preparations should contain at least the minimal therapeutic amount per dose. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 0.0)1% to about 80% of the weight of the unit. The amount of particles containing the active compound(s) in such therapeutically useful compositions is such that a suitable dosage will be obtained.

Techniques and compositions for making useful dosage forms using the present invention are described in one or more of the following references: Anderson, Philip O.; Knoben, James E.; Troutman, William G, eds., Handbook of Clinical Drug Data, Tenth Edition, McGraw-Hill, 2002; Pratt and Taylor, eds., Principles of Drug Action, Third Edition, Churchill Livingston, New York, 1990; Katzung, ed., Basic and Clinical Pharmacology, Ninth Edition, McGraw Hill, 2007; Goodman and Gilman, eds., The Pharmacological Basis of Therapeutics, Tenth Edition, McGraw Hill, 2001; Remington's Pharmaceutical Sciences, 20th Ed., Lippincott Williams & Wilkins., 2000; Martindale, The Extra Pharmacopoeia, Thirty-Second Edition (The Pharmaceutical Press, London, 1999); all of which are incorporated by reference, and the like, relevant portions incorporated herein by reference.

For example, the one or more thyroid hormones may be included in a tablet. Tablets may contain, e.g., suitable binders, lubricants, disintegrating agents, coloring agents, flavoring agents, flow-inducing agents and/or melting agents. For example, oral administration may be in a dosage unit form of a tablet, gelcap, caplet or capsule, the active drug component being combined with an non-toxic, pharmaceutically acceptable, inert carrier such as lactose, gelatin,

agar, starch, sucrose, glucose, methyl cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol, sorbitol, mixtures thereof, and the like. Suitable binders for use with the present invention include: starch, gelatin, natural sugars (e.g., glucose or beta-lactose), corn sweeteners, natural and synthetic gums (e.g., acacia, tragacanth or sodium alginate), carboxymethylcellulose, polyethylene glycol, waxes, and the like. Lubricants for use with the invention may include: sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride, mixtures thereof, and the like. Disintegrators may include: starch, methyl cellulose, agar, bentonite, xanthan gum, mixtures thereof, and the like.

The thyroid hormone(s) or analogs thereof may also be coupled to one or more soluble, biodegradable, bioacceptable polymers as drug carriers or as a prodrug. Such polymers may include: polyvinylpyrrolidone, pyran copolymer, polyhydroxylpropylmethacrylamide-phenol, polyhydroxyethylasparta-midephenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues, mixtures thereof, and the like. Furthermore, the thyroid hormone(s)or analogs thereof may be coupled one or more biodegradable polymers to achieve controlled release of the thyroid hormone(s) or analogs thereof, biodegradable polymers for use with the present invention include: polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacylates, and crosslinked or amphipathic block copolymers of hydrogels, mixtures thereof, and the like.

In one embodiment, gelatin capsules (gelcaps) may include the thyroid hormone(s) or analogs thereof and powdered carriers, such as lactose, starch, cellulose derivatives, magnesium stearate, stearic acid, and the like. Like diluents may be used to make compressed tablets. Both tablets and capsules may be manufactured as immediate-release, mixed-release or modified-release formulations to provide for a range of release of medication over a period of minutes to hours. Compressed tablets may be sugar coated or film coated to mask any unpleasant taste and protect the tablet from the atmosphere. An enteric coating may be used to provide selective disintegration in, e.g., the gastrointestinal tract. Furthermore, these properties can be imparted directly on the particles themselves to achieve the same effect.

For oral administration in a liquid dosage form, the oral drug components may be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water, and the like. Examples of suitable liquid dosage forms include solutions or suspensions in water, pharmaceutically acceptable fats and oils, alcohols or other organic solvents, including esters, emulsions, syrups or elixirs, suspensions, solutions and/or suspensions reconstituted

from non-effervescent granules and effervescent preparations reconstituted from effervescent granules. Such liquid dosage forms may contain, for example, suitable solvents, preservatives, emulsifying agents, suspending agents, diluents, sweeteners, thickeners, and melting agents, mixtures thereof, and the like.

Liquid dosage forms for oral administration may also include coloring and flavoring agents that increase patient acceptance and therefore compliance with a dosing regimen. In general, water, a suitable oil, saline, aqueous dextrose (e.g., glucose, lactose and related sugar solutions) and glycols (e.g., propylene glycol or polyethylene glycols) may be used as suitable carriers for parenteral solutions. Solutions for parenteral administration include generally, a water-soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, buffering salts. Anti-oxidizing agents such as sodium bisulfite, sodium sulfite and/or ascorbic acid, either alone or in combination, are suitable stabilizing agents. Citric acid and its salts and sodium EDTA may also be included to increase stability. In addition, parenteral solutions may include pharmaceutically acceptable preservatives, e.g., benzalkonium chloride, methyl- or propyl-paraben, and/or chlorobutanol. Suitable pharmaceutical carriers are described in Remington's Pharmaceutical Sciences, Mack Publishing Company, a standard reference text in this field, relevant portions incorporated herein by reference.

Capsules. Capsules may be prepared by filling standard two-piece hard gelatin capsules each with 10 to 500 milligrams of particles containing active ingredient.

Soft Gelatin Capsules. Active particles are suspended in a digestible oil such as soybean oil, cottonseed oil or olive oil. The active particles are prepared and injected by using a positive displacement pump into gelatin to form soft gelatin capsules containing, e.g., 10-500 micrograms of the active thyroid hormone. The capsules are washed and dried.

Tablets. A large number of tablets are prepared by conventional procedures so that the dosage unit was 10-500 micrograms of active thyroid hormone, 0.2 milligrams of colloidal silicon dioxide, 5 milligrams of magnesium stearate, 50-275 milligrams of microcrystalline cellulose, 11 milligrams of starch and 98.8 milligrams of lactose. Appropriate coatings may be applied to increase palatability or delay absorption.

To provide an effervescent tablet appropriate amounts of, e.g., monosodium citrate and sodium bicarbonate, are blended together and then roller compacted, in the absence of water, to form flakes that are then crushed to give granulates. The granulates are then combined with the

thyroid hormone(s)particles or analogs thereof, drug and/or salt thereof, conventional beading or filling agents and, optionally, sweeteners, flavors and lubricants.

Injectable solution. A parenteral composition suitable for administration by injection is prepared by stirring 1.5% by weight of thyroid hormone(s) or analogs thereof in deionized water and mixed with, e.g., up to 10% by volume propylene glycol and water. The solution is made isotonic with sodium chloride and sterilized using, e.g., ultrafiltration.

Suspension. An aqueous suspension is prepared for oral administration so that each 5 ml contain 10-500 micrograms of finely divided thyroid hormone(s) or analogs thereof, 200 mg of sodium carboxymethyl cellulose, 5 mg of sodium benzoate, 1.0 g of sorbitol solution, U.S.P., and 0.025 ml of vanillin or suitable flavorant.

For mini-tablets, the active thyroid hormone particles are compressed into a tablet with a hardness in the range 0.5 to 12 Kp. The hardness of the final tablets is influenced by the linear roller compaction strength used in preparing the granulates, which are influenced by the particle size of, e.g., the monosodium hydrogen carbonate and sodium hydrogen carbonate. For smaller particle sizes, a linear roller compaction strength of about 15 to 20 KN/cm may be used.

The present invention also includes pharmaceutical kits useful, for example, for the treatment of hypothyroidism, which comprise one or more containers containing a pharmaceutical composition comprising a therapeutically effective amount of the one or more thyroid hormones. Such kits may further include, if desired, one or more of various conventional pharmaceutical kit components, such as, for example, containers with one or more pharmaceutically acceptable carriers, additional containers, etc., as will be readily apparent to those skilled in the art. Printed instructions, either as inserts or as labels, indicating quantities of the components to be administered, guidelines for administration, and/or guidelines for mixing the components, may also be included in the kit. It should be understood that although the specified materials and conditions are important in practicing the invention, unspecified materials and conditions are not excluded so long as they do not prevent the benefits of the invention from being realized.

In one example, the present invention includes a pharmaceutical composition comprising one or more thyroid hormones or analogs thereof, wherein the first thyroid hormone is formulated for immediate release and the second thyroid hormone is formulated of modified release. For example, the one or more of the thyroid hormones are bound to an ion resin. Non-limiting examples of the one or more thyroid hormones for use with the present invention can be

selected from T4, T3, T4 or T3 N-Methyl, T4 or T3 N-Ethyl, T4 or T3 N-Triphenyl, T4 or T3 N-Propyl, T4 or T3 N-Isopropyl, T4 or T3-N-Tertiary butyl, GC-1, DIPTA, Tetrac and Triac. The two or more thyroid hormones are provided in an amount effective to treat hypothyroidism.

In addition to the two or more thyroid hormones, the composition of the present invention may further comprise one or more biologically active substances that help potentiate the activity of the thyroid hormone(s)s or analogs thereof. Generally, the composition will be adapted for the treatment of hypothyroidism by providing the most common dosage amounts for the equivalent hormone(s).

In one specific embodiment, the two or more thyroid hormones are T4 and/or T3 attached to an ion exchange resin that prevents polymorphism in the crystalline structure. In another example, binding the thyroid hormone to resin provides a geometric dilution to aid in the ease of manufacturing and increase consistency in dosing. Often, the modified release thyroid hormone is T3. The composition of the present invention can be formulated as a liquid suspension, chewable composition, orally disintegrating tablet, or a swallowed tablet composition.

In another specific example, the two or more thyroid hormones are T4 and T3, and are provided a ratio of T4:T3 is from 1:1 to 20:1. These hormones can be provided as a modified release orally disintegrating tablet. For example, the T4, T3, and/or analogs thereof, can be attached to ion-exchange resin particles are acidic cation exchange resins. For example, the ion-exchange resin particles can be basic anion exchange resin. The resin may be further coated, e.g., coating of the one or more modified release drug resin particles comprises a triggered-release coating that is triggered by a pH change. Certain non-limiting examples of coatings for use with the present invention include, e.g., cellulose acetate phthalate, cellulose acetate trimellitate, hydroxypropyl methylcellulose phthalate, polyvinyl acetate phthalate, carboxymethylethylcellulose, co-polymerized methacrylic acid/methacrylic acid methyl esters, co-polymerized methacrylic acid/ acrylic acid ethyl esters, or mixtures thereof. The modified release coating can also be a non-pH dependent controlled release coating.

The dosages of the present invention can vary to meet the needs of an individual user, or can be produced in large batches having specific amounts of the one or more thyroid hormones or equivalents thereof based on the most commonly used amounts. For example, the amount of the one or more thyroid hormones can be from 0.013 to 0.30 mg equivalent of levothyroxine sodium per dose.

The ionic exchange resin and coating can be selected such that greater than 40% of the first thyroid hormone is released within the first 45 minutes after the product is introduced into an in vitro dissolution assay, wherein the conditions of the dissolution assay are an initial dissolution medium of 0.1 N HCL, and after 2 hours, the medium is adjusted to a pH of about 6.8; and the dissolution assay is performed using a USP Apparatus 2.

Another example of the present invention includes a pharmaceutical composition comprising thyroid hormone complexed with ion-exchange resin particles to form drug resin particles, wherein the composition comprises a first plurality of immediate release drug-resin particles and a second plurality of drug-resin particles that are coated for modified release coating, wherein the composition has an *in vivo* fasted serum profile with a first and second peak wherein the first peak occurs before 3 hours after ingestion of the composition and the second peak occurs after 3 hours after ingestion.

Another example of the present invention includes a method of making a pharmaceutical composition comprising: attaching one or more thyroid hormones or analog thereof with ion-exchange resin particles to form drug-resin particles, wherein at least 30 % by weight of the first thyroid hormone or more is formulated for immediate release; and a second thyroid hormone is formulated for modified release.

Another example of the present invention includes a method of evaluating a formulation believed to be useful in treating hypothyroidism, the method comprising: a) measuring the blood levels of one or more thyroid hormone(s) from a first set of subjects suspected of having hypothyroidism; b) administering the formulation to a first subset of the patients, and a placebo to a second subset of the patients; c) repeating step a) after the administration of the formulation or the placebo; and d) determining if the formulation reduces the number of hypothyroidism that is statistically significant as compared to any reduction occurring in the second subset of patients, wherein a statistically significant reduction indicates that the formulation is useful in treating hypothyroidism.

Table 1 – Orally Disintegrating Tablet (ODT)

Example Formulation #1 ODT				
		Amount per dose (mg)		
Ingredient	**Function**	**low**	**high**	
Levothyroxine Sodium	Active T4	0.01300	0.500	
Liothyronine Sodium	Active T3	0.00065	0.500	
Duolite AP143	Exchange Resin	0.00065	33.333	
Methacrylic Acid	DR polymer	0.00163	83.333	Can be used together or separately
Ethylcellulose	XR polymer	0.00007	55.556	
Mannitol		40.0	400.0	
Crospovidone		6.0	60.0	
Microcrystalline Cellulose		4.0	40.0	
Fructose		6.0	200.0	
Flavoring		2.0	10.0	
Colloidal Silicon Dioxide		2.0	20.0	
Triethyl Citrate		2.0	8.0	
Sucralose		2.0	8.0	
Lake Blend Coloring		0.4	2.0	
Magnesium Stearate		0.4	2.0	
Polyethylene Glycol		0.2	1.0	

Table 2 - Tablet

Example Formulation #2 Tablet				
		Amount per dose (mg)		
Ingredient	**Function**	**low**	**high**	
Levothyroxine Sodium	Active T4	0.01300	0.500	
Liothyronine Sodium	Active T3	0.00065	0.500	
Duolite AP143	Exchange Resin	0.00065	33.333	

Methacrylic Acid	DR polymer	0.00163	83.333	Can be used together or separately
Ethylcellulose	XR polymer	0.00007	55.556	
Dibasic Calcium Phosphate		30.0	300.0	
Glyceryl Behebate		10.0	100.0	
Stearyl Alcohol		20.0	200.0	
Micro Crystaline Celluslose		30.0	300.0	
Magnesium Stearate		0.4	2.0	
Polyethylene Glycol		0.2	1.0	

Table 3 Sublingual tablet

Example Formulation #3 Sublingual tablet				
		Amount per dose (mg)		
Ingredient	**Function**	**low**	**high**	
Levothyroxine Sodium	Active T4	0.01300	0.500	
Liothyronine Sodium	Active T3	0.00065	0.500	
Duolite AP143	Exchange Resin	0.00065	33.333	
Methacrylic Acid	DR polymer	0.00163	83.333	Can be used together or separately
Ethylcellulose	XR polymer	0.00007	55.556	
Oleic Acid		0.3	3.0	
Polyethylene Glycol		4.0	20.0	
Silica		4.0	15.0	
Mannitol		20.0	50.0	
Sodium starch glycolate		1.0	3.0	
Sodium stearyl fumarate		0.2	1.5	

Table 4

Example Formulation #4 ODT			
		Amount per dose (mg)	
Ingredient	Function	low	high
Levothyroxine Sodium	Active T4	0.01300	0.500
Liothyronine Sodium	Active T3	0.00065	0.500
Duolite AP143	Exchange Resin	0.00065	33.333
Mannitol		40.0	400.0
Crosspovidone		6.0	60.0
Microcrystalline Cellulose		4.0	40.0
Fructose		6.0	200.0
Flavoring		2.0	10.0
Colloidal Silicon Dioxide		2.0	20.0
Sucralose		2.0	8.0
Lake Blend Coloring		0.4	2.0
Magnesium Stearate		0.4	2.0
Polyethylene Glycol		0.2	1.0

Table 5

Example Formulation #5 Tablet			
		Amount per dose (mg)	
Ingredient	Function	low	high
Levothyroxine Sodium	Active T4	0.01300	0.500
Liothyronine Sodium	Active T3	0.00065	0.500
Duolite AP143	Exchange Resin	0.00065	33.333

Dibasic Calcium Phosphate	30.0	300.0
Stearyl Alcohol	20.0	200.0
Microcrystalline Cellulose	30.0	300.0
Magnesium Stearate	0.4	2.0
Polyethylene Glycol	0.2	1.0

Table 6

Example Formulation #6 Sublingual tablet			
		Amount per dose (mg)	
Ingredient	Function	low	high
Levothyroxine Sodium	Active T4	0.01300	0.500
Liothyronine Sodium	Active T3	0.00065	0.500
Duolite AP143	Exchange Resin	0.00065	33.333
Oleic Acid		0.3	3.0
Polyethylene Glycol		4.0	20.0
Silica		4.0	15.0
Manitol		20.0	50.0
Sodium starch glycolate		1.0	3.0
Sodium stearyl fumarate		0.2	1.5

Table 7 – Orally Disintegrating Tablet (ODT)

Example Formulation #7 ODT				**Modified**	**Modified**
		Amount per dose (mg)			
Ingredient	**Function**	**low**	**high**		
Levothyroxine Sodium	Active T4	0.01300	0.500	**10-100%w/w**	**0-90%w/w**
Liothyronine Sodium	Active T3	0.00065	0.500	**0-90%w/w**	**10-100w/w**
Duolite AP143	Exchange Resin	0.00065	33.333		

Methacrylic Acid	DR polymer	0.00163	83.333	Can be used together or
Ethylcellulose	XR polymer	0.00007	55.556	separately
Mannitol		40.0	400.0	
Crospovidone		6.0	60.0	
Microcrystalline Cellulose		4.0	40.0	
Fructose		6.0	200.0	
Flavoring		2.0	10.0	
Colloidal Silicon Dioxide		2.0	20.0	
Triethyl Citrate		2.0	8.0	
Sucralose		2.0	8.0	
Lake Blend Coloring		0.4	2.0	
Magnesium Stearate		0.4	2.0	
Polyethylene Glycol		0.2	1.0	

w/w=weight to weight

Table 8 - Tablet

Example Formulation #8 Tablet				**Modified**	**Modified**
		Amount per dose (mg)			
Ingredient	**Function**	**low**	**high**		
Levothyroxine Sodium	Active T4	0.01300	0.500	**10-100%w/w**	**0-90%w/w**
Liothyronine Sodium	Active T3	0.00065	0.500	**0-90%w/w**	**10-100w/w**
Duolite AP143	Exchange Resin	0.00065	33.333		
Methacrylic Acid	DR polymer	0.00163	83.333	Can be used together or	
Ethylcellulose	XR polymer	0.00007	55.556	separately	
Dibasic Calcium Phosphate		30.0	300.0		
Glyceryl Behebate		10.0	100.0		
Stearyl Alcohol		20.0	200.0		
Micro Crystaline Celluslose		30.0	300.0		
Magnesium Stearate		0.4	2.0		
Polyethylene Glycol		0.2	1.0		

Table 9 Sublingual tablet

Example Formulation #9 Sublingual tablet				**Modified**	**Modified**
		Amount per dose (mg)			
Ingredient	**Function**	**low**	**high**		
Levothyroxine Sodium	Active T4	0.01300	0.500	**10-100%w/w**	**0-90%w/w**
Liothyronine Sodium	Active T3	0.00065	0.500	**0-90%w/w**	**10-100w/w**
Duolite AP143	Exchange Resin	0.00065	33.333		
Methacrylic Acid	DR polymer	0.00163	83.333	Can be used together or separately	
Ethylcellulose	XR polymer	0.00007	55.556		
Oleic Acid		0.3	3.0		
Polyethylene Glycol		4.0	20.0		
Silica		4.0	15.0		
Mannitol		20.0	50.0		
Sodium starch glycolate		1.0	3.0		
Sodium stearyl fumarate		0.2	1.5		

Table 10

Example Formulation #10 ODT				**Modified**	**Modified**
		Amount per dose (mg)			
Ingredient	Function	low	high		
Levothyroxine Sodium	Active T4	0.01300	0.500	**10-100%w/w**	**0-90%w/w**

Liothyronine Sodium	Active T3	0.00065	0.500	**0-90%w/w**	**10-100w/w**
Duolite AP143	Exchange Resin	0.00065	33.333		
Mannitol		40.0	400.0		
Crosspovidone		6.0	60.0		
Microcrystalline Cellulose		4.0	40.0		
Fructose		6.0	200.0		
Flavoring		2.0	10.0		
Colloidal Silicon Dioxide		2.0	20.0		
Sucralose		2.0	8.0		
Lake Blend Coloring		0.4	2.0		
Magnesium Stearate		0.4	2.0		
Polyethylene Glycol		0.2	1.0		

Table 11

Example Formulation #11 Tablet				**Modified**	**Modified**
		Amount per dose (mg)			
Ingredient	Function	low	high		
Levothyroxine Sodium	Active T4	0.01300	0.500	**10-100%w/w**	**0-90%w/w**
Liothyronine Sodium	Active T3	0.00065	0.500	**0-90%w/w**	**10-100w/w**
Duolite AP143	Exchange Resin	0.00065	33.333		
Dibasic Calcium Phosphate		30.0	300.0		
Stearyl Alcohol		20.0	200.0		
Microcrystalline Cellulose		30.0	300.0		
Magnesium Stearate		0.4	2.0		
Polyethylene Glycol		0.2	1.0		

Table 12

Example Formulation #12 Sublingual tablet				**Modified**	**Modified**
		Amount per dose (mg)			
Ingredient	Function	low	high		
Levothyroxine Sodium	Active T4	0.01300	0.500	**10-100%w/w**	**0-90%w/w**
Liothyronine Sodium	Active T3	0.00065	0.500	**0-90%w/w**	**10-100w/w**
Duolite AP143	Exchange Resin	0.00065	33.333		
Oleic Acid		0.3	3.0		
Polyethylene Glycol		4.0	20.0		
Silica		4.0	15.0		
Manitol		20.0	50.0		
Sodium starch glycolate		1.0	3.0		
Sodium stearyl fumarate		0.2	1.5		

It is contemplated that any embodiment discussed in this specification can be implemented with respect to any method, kit, reagent, or composition of the invention, and vice versa. Furthermore, compositions of the invention can be used to achieve methods of the invention.

It will be understood that particular embodiments described herein are shown by way of illustration and not as limitations of the invention. The principal features of this invention can be employed in various embodiments without departing from the scope of the invention. Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, numerous equivalents to the specific procedures described herein. Such equivalents are considered to be within the scope of this invention and are covered by the claims.

All publications and patent applications mentioned in the specification are indicative of the level of skill of those skilled in the art to which this invention pertains. All publications and patent applications are herein incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference.

The use of the word "a" or "an" when used in conjunction with the term "comprising" in the claims and/or the specification may mean "one," but it is also consistent with the meaning of "one or more," "at least one," and "one or more than one." The use of the term "or" in the claims is used to mean "and/or" unless explicitly indicated to refer to alternatives only or the alternatives are mutually exclusive, although the disclosure supports a definition that refers to only alternatives and "and/or." Throughout this application, the term "about" is used to indicate that a value includes the inherent variation of error for the device, the method being employed to determine the value, or the variation that exists among the study subjects.

As used in this specification and claim(s), the words "comprising" (and any form of comprising, such as "comprise" and "comprises"), "having" (and any form of having, such as "have" and "has"), "including" (and any form of including, such as "includes" and "include") or "containing" (and any form of containing, such as "contains" and "contain") are inclusive or open-ended and do not exclude additional, unrecited elements or method steps. In embodiments of any of the compositions and methods provided herein, "comprising" may be replaced with "consisting essentially of" or "consisting of". As used herein, the phrase "consisting essentially of" requires the specified integer(s) or steps as well as those that do not materially affect the character or function of the claimed invention. As used herein, the term "consisting" is used to indicate the presence of the recited integer (e.g., a feature, an element, a characteristic, a property, a method/process step or a limitation) or group of integers (e.g., feature(s), element(s), characteristic(s), propertie(s), method/process steps or limitation(s)) only.

The term "or combinations thereof" as used herein refers to all permutations and combinations of the listed items preceding the term. For example, "A, B, C, or combinations thereof" is intended to include at least one of: A, B, C, AB, AC, BC, or ABC, and if order is important in a particular context, also BA, CA, CB, CBA, BCA, ACB, BAC, or CAB. Continuing with this example, expressly included are combinations that contain repeats of one or more item or term, such as BB, AAA, AB, BBC, AAABCCCC, CBBAAA, CABABB, and so forth. The skilled artisan will understand that typically there is no limit on the number of items or terms in any combination, unless otherwise apparent from the context.

As used herein, words of approximation such as, without limitation, "about", "substantial" or "substantially" refers to a condition that when so modified is understood to not necessarily be absolute or perfect but would be considered close enough to those of ordinary skill in the art to warrant designating the condition as being present. The extent to which the description may

vary will depend on how great a change can be instituted and still have one of ordinary skilled in the art recognize the modified feature as still having the required characteristics and capabilities of the unmodified feature. In general, but subject to the preceding discussion, a numerical value herein that is modified by a word of approximation such as "about" may vary from the stated value by at least ±1, 2, 3, 4, 5, 6, 7, 10, 12 or 15%.

All of the compositions and/or methods disclosed and claimed herein can be made and executed without undue experimentation in light of the present disclosure. While the compositions and methods of this invention have been described in terms of preferred embodiments, it will be apparent to those of skill in the art that variations may be applied to the compositions and/or methods and in the steps or in the sequence of steps of the method described herein without departing from the concept, spirit and scope of the invention. All such similar substitutes and modifications apparent to those skilled in the art are deemed to be within the spirit, scope and concept of the invention as defined by the appended claims.

What is claimed is:

1. A pharmaceutical composition comprising one or more thyroid hormones or analogs thereof, wherein a first portion of thyroid hormone is formulated for modified release and a second portion of the one or more thyroid hormones is formulated for modified release, wherein the combination of the first and second portion are provided in an amount effective to treat hypothyroidism.

2. The composition of claim 1, wherein the first portion is a T3 thyroid hormone provided at 1-50% modified release, and the second portion is a T4 thyroid hormone provided at 50-99% modified release.

3. The composition of claim 1, wherein the first portion is a T4 thyroid hormone provided at 50-99% modified release, and the second portion is a T3 thyroid hormone provided at 1-50% modified release.

4. The composition of claim 1, wherein the first portion is a T3 and T4 thyroid hormone provided at 10-90% modified release, and the second portion is a T3 and T4 thyroid hormone provided at 90-10% modified release.

5. The composition of claim 1, wherein at least one of the thyroid hormone(s) are bound to an ion resin, the one or more thyroid hormones are selected from at least one of T4, T3, T4 or T3 N-Methyl, T4 or T3 N-Ethyl, T4 or T3 N-Triphenyl, T4 or T3 N-Propyl, T4 or T3 N-Isopropyl, T4 or T3-N-Tertiary butyl, GC-1, DIPTA, Tetrac, or Triac, and optionally the modified release thyroid hormone is T3.

6. The composition of claim 1, wherein the composition further comprises one or more pharmaceutically acceptable carriers, one or more additional biologically active substances, and wherein the composition is adapted for the treatment of hypothyroidism.

7. The composition of claim 1, wherein at least one of the thyroid hormones is T4 or T3, and the ion exchange resin prevents polymorphism in the crystalline structure of the bound hormone.

8. The composition of claim 1, wherein the binding of thyroid hormone to resin provides a geometric dilution to aid in the ease of manufacturing and increase consistency in dosing.

9. The composition of claim 1, wherein the composition is a liquid suspension, chewable composition, orally disintegrating tablet, sublingual, a modified release orally disintegrating tablet, or a swallowed tablet composition.

10. The composition of claim 1, wherein the one or more thyroid hormones are T4 and T3, and are provided a ratio of T4:T3 is from 1:1 to 20:1.

11. The composition of claim 1, wherein the ion-exchange resin particles are an acidic cation exchange resin, a basic anion exchange resin, and they are optionally coated with a triggered-release coating that is triggered by a pH change or a non-pH dependent controlled release coating.

12. The composition of claim 1, wherein the composition is coated and the coating is selected from at least one of cellulose acetate phthalate, cellulose acetate trimellitate, hydroxypropyl methylcellulose phthalate, polyvinyl acetate phthalate, carboxymethylethylcellulose, co-polymerized methacrylic acid/methacrylic acid methyl esters, co-polymerized methacrylic acid/ acrylic acid ethyl esters, or mixtures thereof.

13. The composition of claim 1, wherein the amount of the one or more thyroid hormones is from 0.013 to 0.30 mg equivalent of levothyroxine sodium per dose.

14. The composition of claim 1, wherein greater than 40%, 50%, 60%, 70%, or 80% of the first thyroid hormone is released within the first 45 minutes after the product is introduced into an in vitro dissolution assay, wherein the conditions of the dissolution assay are an initial dissolution medium of 0.1 N HCl, and after 2 hours, the medium is adjusted to a pH of about 6.8, and the dissolution assay is performed using a USP Apparatus 2.

15. The composition of claim 1, wherein the composition consists essentially of at least two thyroid hormones or analogs thereof, wherein a first thyroid hormone or analogs thereof is formulated for immediate release and wherein a second thyroid hormone or analogs thereof is bound to ion resin particles, wherein the drug-resin particles may be uncoated or coated with an immediate release coating, wherein at least 80% of the drug is released within one hour, and wherein the one or more thyroid hormones are selected from at least one of T4, T3, T4 or T3 N-Methyl, T4 or T3 N-Ethyl, T4 or T3 N-Triphenyl, T4 or T3 N-Propyl, T4 or T3 N-Isopropyl, T4 or T3-N-Tertiary butyl, GC-1, DIPTA, Tetrac, or Triac.

16. A pharmaceutical composition comprising thyroid hormone(s) complexed with ion-exchange resin particles to form drug resin particles, wherein the composition comprises a first plurality of immediate release drug-resin particles and a second plurality of drug-resin particles that are coated for modified release, wherein the composition has an *in vivo* fasted serum profile with a first and second peak wherein the first peak occurs before 3 hours after ingestion of the composition and the second peak occurs after 3 hours after ingestion.

17. A method of making a pharmaceutical composition comprising:

attaching a first portion of a first thyroid hormone or analogs thereof to ion-exchange resin particles to form drug-resin particles;

attaching a second portion of a second thyroid hormone or analogs thereof to ion-exchange resin particles to form drug-resin particles; and

wherein at least 10-90% or more by weight of the first portion of thyroid hormone(s) is formulated for modified release, and at least 90-10% or more by weight of the second portion of thyroid hormone(s) is formulated for modified release, wherein the first and second portions are provided in an amount effective to treat hypothyroidism.

18. The method of claim 17, wherein the one or more thyroid hormones are selected from T4, T3, T4 or T3 N-Methyl, T4 or T3 N-Ethyl, T4 or T3 N-Triphenyl, T4 or T3 N-Propyl, T4 or T3 N-Isopropyl, T4 or T3-N-Tertiary butyl, GC-1, DIPTA, Tetrac and Triac, and optionally the modified release thyroid hormone is T3.

19. The method of claim 17, wherein the composition further comprises one or more pharmaceutically acceptable carriers, one or more additional biologically active substances, and wherein the composition is adapted for the treatment of hypothyroidism.

20. The method of claim 17, wherein at least one of the thyroid hormones is T4 or T3, and ion exchange resin prevents polymorphism in the crystalline structure of the bound hormone.

21. The method of claim 17, further comprising binding of thyroid hormone to resin provides a geometric dilution to aid in the ease of manufacturing and increase consistency in dosing.

22. The method of claim 17, further comprising formulating the composition as a liquid suspension, a chewable composition, an orally disintegrating tablet, a sublingual tablet, a modified release orally disintegrating tablet, or a swallowed tablet.

23. The method of claim 17, wherein the one or more thyroid hormones are T4 and T3, and are provided a ratio of T4:T3 is from 1:1 to 20:1.

24. The method of claim 17, wherein the resin particles are ion-exchange resin particles selected from at least one of an acidic cation exchange resin or a basic anion exchange resin, and the resin particles are optionally coated with a triggered-release coating that is triggered by a pH change or a non-pH dependent controlled release coating.

25. The method of claim 17, further comprising coating the composition with a coating selected at least one of cellulose acetate phthalate, cellulose acetate trimellitate, hydroxypropyl methylcellulose phthalate, polyvinyl acetate phthalate, carboxymethylethylcellulose, co-polymerized methacrylic acid/methacrylic acid methyl esters, co-polymerized methacrylic acid/ acrylic acid ethyl esters, or mixtures thereof.

26. The method of claim 17, wherein the amount of the one or more thyroid hormones is from 0.013 to 0.30 mg equivalent of levothyroxine sodium per dose.

27. The method of claim 17, wherein greater than 40%, 50%, 60%, 70%, or 80% of the first thyroid hormone is released within the first 45 minutes after the product is introduced into an in vitro dissolution assay, wherein the conditions of the dissolution assay are an initial dissolution medium of 0.1 N HCl, and after 2 hours, the medium is adjusted to a pH of about 6.8, and the dissolution assay is performed using a USP Apparatus 2.

28. The method of claim 17, wherein a second portion of thyroid hormone provided for modified release comprises greater than 10% by weight.

29. The method of claim 17, further comprising attaching thyroid hormone(s) or analogs thereof to ion-exchange resin particles to form drug-resin particles, wherein there is at least 30% or more weight gain in the drug-resin particles.

30. A method of evaluating a formulation believed to be useful in treating hypothyroidism, the method comprising:

(a) measuring the blood levels of one or more thyroid hormones from a first set of subjects suspected of having hypothyroidism;

(b) administering the formulation to a first subset of the patients, and a placebo to a second subset of the patients, wherein the formulation comprises a first portion of thyroid hormone is formulated for modified release and a second portion of the one or more thyroid hormones is formulated for modified release, wherein the combination of the first and second portion are provided in an amount effective to treat hypothyroidism;

(c) repeating step (a) after the administration of the formulation or the placebo; and

(d) determining if the formulation reduces the number of hypothyroidism that is statistically significant as compared to any reduction occurring in the second subset of patients, wherein a statistically significant reduction indicates that the formulation is useful in treating hypothyroidism.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2018/058922

A. CLASSIFICATION OF SUBJECT MATTER

A61K 47/54 (2017.01) A61K 9/00 (2006.01) A61K 31/00 (2006.01) A61K 31/197 (2006.01) A61P 5/14 (2006.01)

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)

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)

Databases: EPOQUE: PATENW; STN: HCAPLUS, BIOSIS, EMBASE, MEDLINE. Keywords: Thyroid hormone, T3, T4, thyroxine, Triiodothyronine, drug resin, ionic exchange, cationic exchange, anionic exchange, duolite, AP143-1083, extended release or controlled release and like terms. CPC mark A61K47/51/LOW was used in Patenw. Applicant and inventor name searches were conducted using internal IPA databases PAMS NOSE and INTESS and public databases ESPACENET and PUBMED, with or without keywords as above.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	Documents are listed in the continuation of Box C	

[X] Further documents are listed in the continuation of Box C [X] See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 February 2019	08 February 2019
Name and mailing address of the ISA/AU	**Authorised officer**
AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA Email address: pct@ipaustralia.gov.au	Holly Thomas AUSTRALIAN PATENT OFFICE (ISO 9001 Quality Certified Service) Telephone No. +61262256157

INTERNATIONAL SEARCH REPORT C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		International application No. **PCT/US2018/058922**
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2004/0152783 A1 (LAWRENCE PETER OLON et al.) 05 August 2004 Abstract; [0001]; [0027]-[0029]; [035]; [0036].	1-30
X	US 2009/0011027 A1 (YASHWANT VISHNUPANT PATHAK et al.) 08 January 2009 Abstract; [0008]; [0010]-[0011]; [0015]; [0018]; [0020].	1-30
X	US 2008/0118570 A1 (ZHI LIU et al.) 22 May 2008 Abstract; [0012]; [0039]; [0040]; [0100]; [0106].	1-30
X	US 2005/0181050 A1 (JANE HIRSH et al.) 18 August 2005 Abstract; [0010]-[0016]; [0035]; [0041]; [0050]-[0080]; [0099].	1-30
X	WO 2006/081518 A2 (COLLEGIUM PHARMACEUTICAL, INC.) 03 August 2006 Abstract; Page 5, Lines 12-27; Page 10, Lines 4-14; Page 13, Lines 16-24; "Coatings" starting Page 16.	1-30
P,X	WO 2017 /192458 A1 (SPECTRIX THERAPEUTICS, LLC) 09 November 2017 Whole document, particularly the abstract; Page 1, Line 29 – Page 4, Line 19; Page 4, Para. 2; Tables 1-6.	1-30

INTERNATIONAL SEARCH REPORT Information on patent family members	International application No. **PCT/US2018/058922**

This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document/s Cited in Search Report		**Patent Family Member/s**	
Publication Number	**Publication Date**	**Publication Number**	**Publication Date**
US 2004/0152783 A1	05 August 2004	US 2004152783 A1	05 Aug 2004
		AU 2003290613 A1	07 Jun 2004
		EP 1565171 A2	24 Aug 2005
		WO 2004041208 A2	21 May 2004
US 2009/0011027 A1	08 January 2009	US 2009011027 A1	08 Jan 2009
		US 8313770 B2	20 Nov 2012
		CA 2689101 A1	11 Dec 2008
		EP 2164631 A1	24 Mar 2010
		JP 2010529040 A	26 Aug 2010
		MX 2009013019 A	01 Apr 2010
		WO 2008151071 A1	11 Dec 2008
US 2008/0118570 A1	22 May 2008	US 2008118570 A1	22 May 2008
		WO 2008064163 A2	29 May 2008
US 2005/0181050 A1	18 August 2005	US 2005181050 A1	18 Aug 2005
		CA 2596035 A1	03 Aug 2006
		EP 1846040 A2	24 Oct 2007
		US 2005255048 A1	17 Nov 2005
		US 2007036843 A1	15 Feb 2007
		US 2007232695 A1	04 Oct 2007
		WO 2005115336 A2	08 Dec 2005
		WO 2006081518 A2	03 Aug 2006
WO 2006/081518 A2	03 August 2006	WO 2006081518 A2	03 Aug 2006
		CA 2596035 A1	03 Aug 2006
		EP 1846040 A2	24 Oct 2007
		US 2005181050 A1	18 Aug 2005
		US 2005255048 A1	17 Nov 2005
		US 2007036843 A1	15 Feb 2007
		US 2007232695 A1	04 Oct 2007
		WO 2005115336 A2	08 Dec 2005
WO 2017 /192458 A1	09 November 2017	None	

End of Annex

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.