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(54) Title: LIQUID PHARMACEUTICAL COMPOSITIONS COMPRISING THYROID HORMONES

(57) Abstract

There is disclosed a liquid pharmaceutical composition comprising a therapeutic agent which comprises: one or more thyroid hormone or hormones; from about 40 % to about 96 % ethanol by volume; a pH adjusting agent so that the measured pH of the composition is from about 9 to about 12; and from about 4 % to about 50 % water by volume; which has utility in the treatment of disorders associated with an impairment of the thyroid hormone function in animals including human beings. The liquid composition may be delivered by a metered dosage delivery system such as an aerosol or pump-action spray.

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LIQUID PHARMACEUTICAL COMPOSITIONS COMPRISING THYROID HORMONES

This invention relates to novel pharmaceutical compositions comprising at least one thyroid hormone and their derivatives, and to their use in the treatment of disorders associated with impairment of the thyroid hormone functions in animals including human beings.

Many patients, particularly the elderly or small children may have difficulty swallowing traditional oral dosage forms. For these patients liquid dosage forms may result in increased patient compliance. Liquid dosage forms may also have the advantage of more reproducible bioavailability over solid dosage forms. However, liquid oral dosage forms (such as solutions, syrups and suspensions) comprising thyroid hormones are difficult to dose accurately due to the small (microgram) quantities of active ingredient. For these reasons products in liquid oral dosage form comprising thyroid hormones are not currently available. Therefore it is an object of the present invention to provide a liquid dosage form and delivery system for thyroid hormone which has improved patient compliance over traditional solid oral dosage forms, which can accurately deliver small doses of thyroid hormone, and which has a suitably long shelf life.

Thyroid hormones comprise one or more of the following:
L-3,5,3',5'-tetraiodothyronine (levothyroxine or LT4);
L-3,5,3'-triiodothyronine (liothyronine or LT3);
L-3,3',5'-triiodothyronine (LrT3);
L-3,5-diiodothyronine (LT2); or any mixtures thereof.
As used herein the term thyroid hormone should be

understood to include pharmaceutically acceptable salts thereof, preferably sodium salts.

Thyroid hormones as described herein are useful in the treatment of disorders associated with improvement of the thyroid hormone function in animals including human beings for example, myxedema, cretinism or obesity. Thyroid hormones can be prepared synthetically as the biologically active l-enantiomer or can be isolated directly from the thyroid gland of animals.

Solutions are a highly useful means of administering accurately metered doses of drug substances. However, thyroid hormones are known to be unstable in solution and are not normally sufficiently soluble in water for the intended purpose. Surprisingly, it has been discovered that an ethanolic aqueous solution can form the basis of a stable solution comprising thyroid hormones suitable for use in liquid formulations which can be delivered in metered doses.

Therefore the present invention provides a liquid pharmaceutical composition comprising a therapeutic agent which comprises at least one thyroid hormone; from about 40% to about 96% ethanol by volume; a pH adjusting agent so that the measured pH of the composition is from about 9 to about 12; and from about 4% to about 50% water by volume.

'By volume' throughout the specification and claims indicates a percentage is the volume of a liquid ingredient per total volume of the liquid composition. 'By mass' indicates a percentage is the mass of an ingredient per total mass of the composition.

Thyroid hormones may exist as one or more polymorphic forms (for example one or more crystalline forms, amorphous forms, phases, solid solutions and/or mixtures thereof), and the therapeutic agent may include and pharmaceutically acceptable polymorphic forms of thyroid hormones and/or mixtures thereof.

Thyroid hormones may also exist in the forms of solvates (for example hydrates) and the therapeutic agent may include each solvate of the thyroid hormones and/or mixtures thereof.

Preferably the thyroid hormone is present in the compositions in an amount per unit dose from about 0.1 μg to about 10,000 μg, more preferably from about 1 μg to about 1000 μg, most preferably if the thyroid hormone is LT_4 from about 25 μg to about 300 μg. It will be readily appreciated that the doses of thyroid hormone will vary according to which thyroid hormone or derivative is used and will therefore be adjusted accordingly.

Preferably the volume of the composition per unit dose is about 0.1 μl to about 10,000 μl, more preferably from about 1 μl to about 1,000 μl, most preferably if the thyroid hormone is LT_4 from about 10 μl to about 600 μl.

The concentration of thyroid hormone in liquid compositions of the invention will vary according to the unit dose or volume desired and which thyroid hormone derivative is used. However, typically if the thyroid hormone is LT_4 the concentration will be from about 0.1 mg ml^{-1} to about 1.0 mg ml^{-1}.

Preferably the ethanol is present in an amount from about 50% to about 80%, more preferably from about 60% to about 75%, by volume of the composition.

Preferably the composition further comprises from a trace amount to about 5% by mass of a pharmaceutically acceptable sequestrating agent which may be an ethylene diamine tetra-acetate salt (eg a sodium salt).

Preferably the composition additionally comprises from a trace amount to about 5% by mass of an pharmaceutically acceptable antioxidant which may be a metabisulphite or sulphite salt (eg a sodium salt).

Preferably the pH adjusting agent is sodium hydroxide and the measured pH of the formulation is from about 9 to about 11, more preferably about 10. It will be readily appreciated by persons skilled in the art that a pH measured in a non-aqueous solvent by a suitable means (for example a pH meter) is not to be considered to relate directly to hydrogen ion concentration but is to be used for comparative purposes only.

The liquid composition of the present invention may further comprise one or more of the following pharmaceutically acceptable optional ingredients:
colouring agents, for example conventional pharmaceutically acceptable dyes;
orally acceptable preservatives, for example benzyl alcohol, sodium hypochlorite, phenoxy ethanol and/or propylene glycol;
sweetening agents for example glycerin, sucrose, sorbitol, sodium saccharin and/or aspartame;
flavouring agents, for example sodium citrate and/or citric acid; and

thickening agents, for example povidone and/or hydroxypropyl methylcellulose.

These optional ingredients may be present in an amount from a trace amount to about 40% by mass of the composition, preferably (if the optional ingredient is other than glycerin) from a trace amount to about 10% by mass.

The formulation of the present invention is suitable for use in a metered dosage delivery system such as a pump-action spray or a pressurised aerosol can, in which the propellent is preferably free of oxygen.

Therefore a further aspect of the invention provides a metered dosage delivery system which comprises a liquid composition as described herein.

A further aspect of the present invention provides use of a thyroid hormone in the preparation of the pharmaceutical compositions described herein for the treatment of disorders associated with an impairment of the thyroid hormone function in animals including human beings.

A still further aspect of the present invention provides a method of treating disorders associated with an impairment of the thyroid hormone function in animals including human beings, which comprises administering to a patient in need thereof a therapeutically and/or prophylactically effective amount of the pharmaceutical compositions described herein.

Whilst the precise amount of the therapeutic agent administered in the treatment described outlined above

will depend on a number of factors, for example the severity of the condition, the age and past medical history of the patient, and always lies within the sound discretion of the administering medical practioner or veterinary a suitable daily dose of a thyroid hormone for administration to animals, preferably human beings, may generally be from about 0.1 μg to about 10,000 μg, preferably from about 1 μg to about 1,000 μg, more preferably if the thyroid hormone is LT_4 from about 25 μg to about 300 μg, given in a single dose or in divided doses at one or more times during the day.

Liquid compositions of the present invention provide a versatile means in which to administer a unit dose of the therapeutic agent. For example when the therapeutic agent is LT_4, the liquid dosage form may comprise a spray or aerosol comprising a solution having a concentration of LT_4 of 1 mg ml^{-1}. Preferably the spray delivers a volume of solution per unit dose of from about 25 μl to about 300 μl (equivalent to a dose of from about 25 μg to about 300 μg). If the spray comprises a solution having a concentration of LT_4 of 0.5 mg ml^{-1} then preferably the spray delivers a volume of solution per unit dose of from about 50 μl to 600 μl (equivalent to a dose of from about 25 μg to about 300 μg of LT_4).

Pharmaceutical compositions of the present invention may be used in adjunctive therapy with one or more other compounds having activity in the treatment of disorders associated with an impairment of the thyroid hormone function in animals including human beings. It will be appreciated that the term treatment as used herein includes prophylactic use of the pharmaceutical compositions of the present invention, for example to

protect against conditions such as hypothyroidism, in animals including human beings.

The invention will now be illustrated by the following non-limiting examples. Throughout the examples % m/v indicates the percentage in the amount of ingredient by mass (g) per volume of the composition (ml) and % v/v indicates the percentage in the amount of ingredient by volume.

Example 1

Ingredient	% m/v
Levothyroxine sodium (LT_4)	0.1
EDTA (Sequestrine NA4)	0.05
Sodium metabisulphite	0.05
Sodium saccharin	0.10
Ethanol	70 (% v/v)
Purified water to . . .	100

The above ingredients were mixed together to form an ethanolic solution which had a pH, measured with a pH meter, of 9.3. The solution was filtered and sealed in ampoules, the headspace being air.

The stability of the therapeutic agent (LT_4) in this formulation was tested with the formulation held at various temperatures over 6 months. The results are tabulated below, as a fraction of LT_4 remaining. A dash indicates that no data are available for the amount of LT_4 present at a particular temperature after a particular duration.

	Duration					
Temp° C	Init-ially	After 2 weeks	1 month	2 months	3 months	6 months
4	0.97	-	-	0.99	1.00	1.09
25	0.97	1.01	1.00	0.99	1.00	1.07
30	0.97	-	-	0.99	-	1.07
40	0.97	-	-	-	0.97	1.00
50	0.97	1.03	0.94	-	0.88	0.81

Examples 2 to 3

Ingredient	% m/v
Levothyroxine sodium (LT_4)	0.1
EDTA (Sequestrene NA4)	0.05
Sodium sulphite	0.05
Glycerin	30.0 (% v/v)
Ethanol	40.0 (% v/v)
Purified water to . . .	100

The above ingredients were mixed to form a solution as in Example 1, which had a pH, measured with a pH meter, of 9.3. The stability results over 3 months for this solution filled into ampoules having either an air (Example 2) or nitrogen (Example 3) headspace are given in the following table, as a fraction of LT_4 remaining.

	Duration			
Temp° C	Init-ially	1 month	2 months	3 months
Example 2 - Ampoule (air)				
4	0.97	0.99	0.99	0.97
25	0.97	0.98	0.98	0.95
40	0.97	0.99	0.95	0.80
50	0.97	0.97	0.83	0.68
Example 3 - Ampoule (nitrogen)				
4	0.98	0.99	1.00	0.97
25	0.98	0.99	0.99	0.97
40	0.98	0.98	0.98	0.95
50	0.98	0.99	0.96	0.93

Examples 4 to 6

Ingredient	% m/v
Levothyroxine sodium	0.1
EDTA (Sequestrene NA4)	0.05
Sodium sulphite	0.05
Ethanol	70 (% v/v)
Purified water to . . .	100

The above ingredients were mixed to form a solution as in Example 1, which had a pH, measured with a pH meter, of 10.1. The stability results are tabulated below in a similar manner to Examples 1 to 3 above for a solution filled into ampoules and having an air (Example 4) or a nitrogen (Example 5) headspace. Stability results for a solution prepared as above (with a measured pH of 10.0) which was filled into a pump pack

(Example 6) is also given in the following table. A dash indicates no data are available.

	Duration				
Temp °C	Init-ially	1 month	2 months	3 months	6 months
Example 4 (Ampoule - air)					
4	1.01	0.99	1.0	0.99	0.98
25	1.01	1.00	0.95	0.99	0.99
40	1.01	0.99	0.99	0.97	0.94
50	1.01	0.96	0.95	0.89	0.84
Example 5 (Ampoule - nitrogen)					
4	1.01	1.04	1.01	1.01	1.00
25	1.01	1.00	1.01	0.99	1.00
40	1.01	1.00	1.01	0.99	1.00
50	1.01	0.99	0.99	0.96	0.95
Example 5 (Pump pack)					
4	1.02	1.03	-	1.03	-
25	1.02	1.04	-	1.04	-
40	1.02	1.01	-	1.05	-
50	1.02	1.00	-	0.99	-

Examples 7 to 9

Ingredient	% m/v
Levothyroxine sodium	0.1
EDTA (Sequestrine NA4)	0.05
Sodium sulphite	0.1
Ethanol	70 (% v/v)
Purified water to . . .	100

The above ingredients were mixed as in Example 1 to produce a solution with a measured pH of 10.3, which was then stored as described in Examples 4 to 6. The stability results are as follows. A dash indicates no data are available.

	Duration				
Temp °C	Init-ially	1 month	2 months	3 months	6 months
Example 7 (Ampoule - air)					
4	1.00	0.99	1.01	1.01	1.00
25	1.00	0.99	1.00	0.99	0.98
40	1.00	0.98	0.99	0.96	0.97
50	1.00	0.96	0.965	0.91	0.86
Example 8 (Ampoule - nitrogen)					
4	1.01	0.99	1.01	1.00	1.01
25	1.01	0.99	1.01	1.00	1.00
40	1.01	0.99	1.00	1.00	1.01
50	1.01	0.99	1.01	0.99	0.97
Example 9 (Pump pack)					
4	1.03	1.02	-	1.02	-
25	1.03	1.02	-	1.03	-
40	1.03	1.03	-	1.04	-
50	1.03	1.01	-	0.99	-

Examples 10 to 12

Ingredient	% m/v
Levothyroxine sodium	0.1
EDTA (Sequestrene NA4)	0.05
Sodium sulphite	0.1
Sodium saccharin	0.1
Ethanol	70 (% v/v)
Purified water to . . .	100

The above ingredients were mixed as in Example 1 to produce a solution with a measured pH of 10.2 and 10.3, which was then stored as described in Examples 4 to 6. The stability results are as follows. A dash indicates no data are available.

	Duration				
Temp °C	Init-ially	1 month	2 months	3 months	6 months
Example 10 (Ampoule - air)					
4	0.95	1.04	0.95	0.95	0.97
25	0.95	1.04	0.96	0.92	0.94
40	0.95	1.03	0.95	0.90	0.93
50	0.95	1.00	0.90	0.83	0.81
Example 11 (Ampoule - nitrogen)					
4	0.96	1.05	0.96	0.97	0.97
25	0.96	1.06	0.99	0.93	0.95
40	0.96	1.06	0.97	0.93	0.98
50	0.96	1.06	0.97	0.91	0.92
Example 12 (Pump pack)					
4	0.99	1.04	-	0.99	-
25	0.99	1.03	-	1.00	-
40	0.99	1.05	-	0.99	-
50	0.99	1.02	-	0.95	-

Claims

1. A liquid pharmaceutical composition comprising a therapeutic agent which comprises at least one thyroid hormone; from about 40% to about 96% ethanol by volume; a pH adjusting agent so that the measured pH of the composition is from about 9 to about 12; and from about 4% to about 50% water by volume.

2. A composition as claimed in claim 1, in which the thyroid hormone comprises:
L-3,5,3',5'-tetraiodothyronine (levothyroxine or LT4);
L-3,5,3'-triiodothyronine (liothyronine or LT3);
L-3,3',5'-triiodothyronine (LrT3);
L-3,5-diiodothyronine (LT2);
pharmaceutically acceptable salts thereof; or any mixtures thereof.

3. A composition as claimed in any preceding claim, in which the ethanol is present in an amount from about 50% to about 80% by volume of the composition.

4. A composition as claimed in any preceding claim, which further comprises from a trace amount to about 5% by mass of the composition of a pharmaceutically acceptable sequestrating agent.

5. A composition as claimed in any preceding claim, which further comprises from a trace amount to about 5% by mass of the composition of a pharmaceuticall acceptable anti-oxidant.

6. A metered dosage delivery system which comprises a composition as claimed in any preceding claim.

7. Use of a thyroid hormone in the preparation of a composition as claimed in any of claims 1 to 5, for the treatment of disorders associated with an impairment of the thyroid hormone function in animals including human beings.

8. A method of treating disorders associated with an impairment of the thyroid hormone function in animals including human beings, which comprises administration to a patient in need thereof of a therapeutically or prophylactically effective amount of a composition as claimed in any of claims 1 to 5.

9. A method for preparing a liquid pharmaceutical composition comprising a therapeutic agent comprising combining at least one thyroid hormone with from about 40% to about 96% ethanol by volume; a pH adjusting agent so that the measured pH of the composition is from about 9 to about 12; and from about 4% to about 50% water by volume.

10. A method as claimed in claim 9, in which the thyroid hormone comprises:
L-3,5,3',5'-tetraiodothyronine (levothyroxine or LT4);
L-3,5,3'-triiodothyronine (liothyronine or LT3);
L-3,3',5'-triiodothyronine (LrT3);
L-3,5-diiodothyronine (LT2);
pharmaceutically acceptable salts thereof; or any mixtures thereof.

11. A method as claimed in either claim 9 or 10, in which the ethanol is added to the composition in an amount from about 50% to about 80% by volume of the composition.

12. A method as claimed in any of claims 9 to 11, which further comprises adding to the composition from a trace amount to about 5% by mass of the composition of a pharmaceutically acceptable sequestrating agent.

13. A method as claimed in any of claims 9 to 12, which further comprises adding to the composition from a trace amount to about 5% by mass of the composition of a pharmaceutically acceptable anti-oxidant.

14. A method for preparing metered dosage delivery system comprising filling the delivery system with a liquid composition as claimed in any of claims 1 to 5.

15. Use of a thyroid hormone in a method as claimed in any of claims 9 to 13, for preparing a liquid pharmaceutical composition for treating disorders associated with an impairment of the thyroid hormone function in animals including human beings.

INTERNATIONAL SEARCH REPORT

Interna ! Application No
PCT/EP 95/00323

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/195 A61K9/00 A61K47/10

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)
IPC 6 A61K

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DE,A,25 46 474 (M.ISRAEL) 21 April 1977 see claims see page 8, line 3 ---	1-15
A	GB,A,2 191 695 (THE HOSPITAL ATTACHED TO TIANJIN ACADEMY OF MEDICAL SCIENCES) 23 December 1987 see claims 1-5,14 see examples ---	1-15
A	DATABASE WPI Week 8820, Derwent Publications Ltd., London, GB; AN 88-137257 (20) see abstract & JP,A,63 079 824 (ADVANCE KK) 9 April 1988 --- -/--	1-15

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

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"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
12 May 1995	26. 05. 95

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Scarponi, U

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INTERNATIONAL SEARCH REPORT

Interna ! Application No
PCT/EP 95/00323

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GB,A,923 171 (SMITH KLINE & FRENCH LABORATORIES) 10 April 1963 see claims see example 3 ---	1-15
P,A	CHEMICAL ABSTRACTS, vol. 121, no. 18, 31 October 1994, Columbus, Ohio, US; abstract no. 213005, see abstract & JP,A,06 183 952 (SANYO CHEMICAL IND. LTD.,JAPAN) 5 July 1994 -----	1-15

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 95/00323

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: claim 8
because they relate to subject matter not required to be searched by this Authority, namely:
please see attached sheet ../..

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

Subject-matter excluded from Patentability:
Although claim 8 is directed to a method of treatment of the human body by the rapy (Rule 39.1(IV)PCT), the search has been carried out and based on the alle ged effects of the compositions.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern al Application No
PCT/EP 95/00323

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE-A-2546474	21-04-77	NONE	
GB-A-2191695	23-12-87	US-A- 4870106	26-09-89
JP-A-63079824	09-04-88	NONE	
GB-A-923171		NONE	
JP-A-06183952	05-07-94	NONE	