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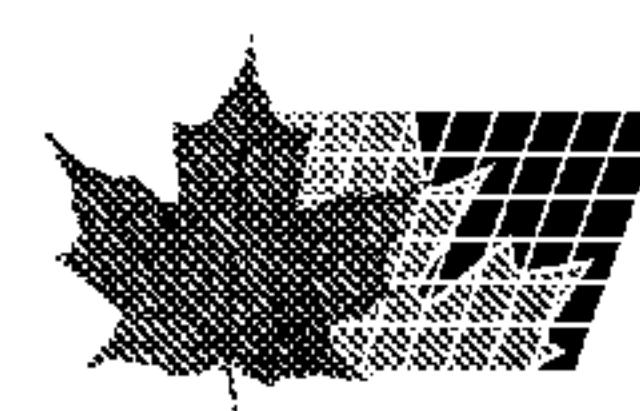
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(54) Title: STABLE FORMULATIONS OF TESTOSTERONE UNDECANOATE

(57) Abrégé/Abstract:

The present invention is directed to stable pharmaceutical formulations. More specifically, the present invention is directed to stable pharmaceutical formulations of testosterone undecanoate.



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(54) Title: STABLE FORMULATIONS OF TESTOSTERONE UNDECANOATE

(57) Abstract: The present invention is directed to stable pharmaceutical formulations. More specifically, the present invention is directed to stable pharmaceutical formulations of testosterone undecanoate.

TITLE OF THE INVENTION

STABLE FORMULATIONS OF TESTOSTERONE UNDECANOATE

FIELD OF THE INVENTION

5 The present invention is directed to stable pharmaceutical formulations. More specifically, the present invention is directed to pharmaceutical formulations of testosterone undecanoate resulting in a reduced food effect and increased exposure.

BACKGROUND OF THE INVENTION

10 Testosterone undecanoate, known as ANDRIOL, has been marketed in many countries for male hypogonadism, since 1978. The first ANDRIOL market formulation was a digestible formulation containing oleic acid. The drawback of this formulation is that it only had a shelf-life of three months at room temperature. The short shelf-life was caused by reesterification of the undecanoate ester with oleic acid. Due to this instability, a new
15 formulation containing castor oil and lauroglycol was developed.

This new formulation is disclosed in US Patent No. 6,652,880 and US Application No. US2005/0287203 and has been on the market in many countries as ANDRIOL TESTOCAPSS since 2003. The ANDRIOL TESTOCAPS formulation is a non-digestible formulation with a shelf-life of 3 years.

20 Testosterone undecanoate has a LogP of 9.1 and very low water solubility. Both ANDRIOL and ANDRIOL TESTOCAPS formulations show an absolute bioavailability of 4% in fed state. Together with a medium to high fat meal, testosterone undecanoate is emulgated in the gastrointestinal tract through a combination of digested fats and bile acids. Once emulgated, testosterone undecanoate is incorporated into the chylomicrons and absorbed via the lymph. In
25 fasted state no elevated testosterone undecanoate and/or testosterone serum levels are obtained. Thus, there is still a need for a stable, preferably low-dose pharmaceutical formulation of testosterone undecanoate that results in increased exposure and a decreased food-effect so that patients can rely on testosterone undecanoate being absorbed in fasted state as well as with low-fat meals.

30 Self-emulsifying formulations of testosterone esters are described in several U.S. patents and applications including: U.S. Patent No. 8,241,664, which describes a self-emulsifying drug delivery system (SEDDS) of testosterone undecanoate using digestible oils, hydrophilic surfactants, and hydrophobic surfactants; U.S. Patent Application Publication No. 2011/0251167 which describes preparation of SEDDS of testosterone undecanoate containing oleic acid,
35 CREMOPHORE RH40, peppermint oil and borage oil; U.S. Patent Application Publication No. 2012/0135069 which describes preparation of nanonized testosterone esters using solid lipid matrix (stearic acid); U.S. Patent Application 2012/0135074 and 2012/0148675 which describe compositions of testosterone undecanoate in various solubilizers to achieve a concentration of

testosterone undecanoate of 14-35% as a solution, mixture of crystalline and solution, and a solid mixture; and U.S. Patent Application No. 20130303495 which describes an emulsion, microemulsion or nanoemulsion formulation for pharmaceutical administration of testosterone undecanoate comprising a digestible lipid, a water-soluble surfactant, a water-insoluble surfactant; 5 a phytosterol and/or phytosterol fatty acid esters, and dl-alpha-tocopherol. However, such formulations do not all achieve a stable, preferably low-dose pharmaceutical formulation of testosterone undecanoate that results in increased exposure and a decreased food-effect so that patients can rely on testosterone undecanoate being absorbed in a fasted state as well as with low-fat meals.

10

SUMMARY OF THE INVENTION

Since both ANDRIOL and ANDRIOL TESTOCAPS formulations are not capable of self-emulgation in watery systems it is expected these formulations show a bad emulgation during fasted state so testosterone undecanoate is not available for incorporation into the 15 chylomicrons. Since the digestible oleic acid ANDRIOL formulation displayed the same food effect as the non-digestible ANDRIOL TESTOCAPS formulation, the inventors anticipated that the lack of emulgation could be the main reason for the observed food effect of both formulations.

Described herein are pharmaceutical formulations comprising self-emulsifying drug delivery systems (SEDDS) comprising testosterone undecanoate, wherein the testosterone undecanoate is capable of forming a self-emulsifying system in an aqueous environment. In certain embodiments of the SEDDS described herein, are self-nanoemulsifying drug delivery systems (SNEDDS). With regard to the description below when SEDDS are discussed, SNEDDS are also contemplated. The SEDDS pharmaceutical formulations described herein have a good solvation capacity for testosterone undecanoate and are able to keep testosterone undecanoate dissolved in the gastrointestinal tract to promote contact between the oily, testosterone undecanoate containing droplets and the chylomicrons which will enter the lymphatics.

The pharmaceutical formulations described herein are designed to alter testosterone bioavailability in the fasted state which may result in less food effect. The 30 pharmaceutical formulations described herein also allow for increased exposure of testosterone. The reduction of food effect and increased exposure may also allow for a lower dose of testosterone undecanoate compared to the ANDRIOL TESTOCAPS.

The pharmaceutical formulations described herein also demonstrate a faster onset 35 (shorter T_{max}) especially in fasted state compared to the ANDRIOL TESTOCAPS. Therefore, a faster and higher extent of absorption is expected with the formulations described herein.

Specifically, described herein are self-emulsifying pharmaceutical formulations comprising testosterone undecanoate, a water soluble surfactant, a non-ionic surfactant and a water insoluble surfactant and, optionally, a digestible long-chain fatty acid ester.

Also described herein are methods for the treatment of hypogonadism comprising 5 administering to a patient in need thereof one of the formulations described herein.

DETAILED DESCRIPTION OF THE INVENTION

Described herein are stable, liquid pharmaceutical formulations comprising 10 testosterone undecanoate in a self-emulsifying drug delivery system (SEDDS), wherein the testosterone undecanoate is capable of forming a self-emulsifying system in an aqueous environment. In certain embodiments, the pharmaceutical formulations described herein comprise testosterone undecanoate, a water soluble surfactant, a non-ionic surfactant and a water insoluble surfactant and, optionally, a digestible long-chain fatty acid ester.

In certain embodiments, the pharmaceutical formulations described herein 15 comprise testosterone undecanoate, a water soluble surfactant, a non-ionic surfactant and a water insoluble surfactant, and a digestible long-chain fatty acid ester. For example, in certain embodiments, the pharmaceutical formulations described herein comprise testosterone undecanoate, propylene glycol, CREMOPHOR EL, CAPRYOL 90 and ethyl oleate.

In certain embodiments, the pharmaceutical formulations described herein 20 comprise testosterone undecanoate; a water soluble surfactant, a non-ionic surfactant and a water insoluble surfactant. For example, in certain embodiments, the pharmaceutical formulations described herein comprise testosterone undecanoate, propylene glycol, CREMOPHOR EL and CAPRYOL 90.

The formulations described herein contain between about 6% to 12% of 25 testosterone undecanoate by weight. In certain embodiments, the formulations described herein, contain 12% or less of testosterone undecanoate by weight. In such embodiments, the amounts of testosterone undecanoate are less than that found in commercial embodiments such as ANDRIOL which contain 12% of testosterone undecanoate by weight. In certain embodiments, the formulations described herein, contain 10% or less of testosterone undecanoate by weight. In certain embodiments, the formulations described herein, contain 9% or less of testosterone undecanoate by weight. In certain embodiments, the formulations described herein, contain 7.5% 30 or less of testosterone undecanoate by weight.

In certain embodiments, the formulations described herein contain about 12% of testosterone undecanoate. In other embodiments, the formulations described herein contain about 35 9% of testosterone undecanoate. In other embodiments, the formulations described herein contain about 7.5% of testosterone undecanoate. In yet other embodiments, the formulations described herein contain about 6% of testosterone undecanoate.

The formulations described herein include a water soluble (hydrophilic) surfactant, a non-ionic surfactant and a water insoluble (hydrophobic) surfactant. The surfactants can be in any ratio that will give the desired properties of the formulations with testosterone undecanoate. In certain embodiments of the formulations described herein the ratio by weight of the water soluble surfactant, a non-ionic surfactant and a water insoluble surfactant is about 1:1:1, 1:2:1, 5 1:3:1, 1:4:1, 1:5:1, 2:1:1, 2:2:1, 2:3:1, 2:4:1, 2:5:1, 3:1:1, 3:2:1, 3:3:1, 3:4:1, 3:5:1, 4:1:1, 4:2:1, 4:3:1, 4:4:1, 4:5:1, 5:1:1, 5:2:1, 5:3:1, 5:4:1 or 5:5:1. In certain embodiments of the 10 formulations described herein the ratio by weight of the water soluble surfactant, a non-ionic surfactant and a water insoluble surfactant is about 1:1:2, 1:2:2, 1:3:2, 1:4:2, 1:5:2, 2:1:2, 2:2:2, 2:3:2, 2:4:2, 2:5:2, 3:1:2, 3:2:2, 3:3:2, 3:4:2, 3:5:2, 4:1:2, 4:2:2, 4:3:2, 4:4:2, 4:5:2, 5:1:2, 5:2:2, 5:3:2, 5:4:2 or 5:5:2. In certain embodiments of the formulations described herein the ratio by weight of the water soluble surfactant, a non-ionic surfactant and a water insoluble surfactant is about 1:1:3, 1:2:3, 1:3:3, 1:4:3, 1:5:3, 2:1:3, 2:2:3, 2:3:3, 2:4:3, 2:5:3, 3:1:3, 3:2:3, 3:3:3, 3:4:3, 15 3:5:3, 4:1:3, 4:2:3, 4:3:3, 4:4:3, 4:5:3, 5:1:3, 5:2:3, 5:3:3, 5:4:3 or 5:5:3. In certain embodiments of the formulations described herein the ratio by weight of the water soluble surfactant, a non-ionic surfactant and a water insoluble surfactant is about 1:1:4, 1:2:4, 1:3:4, 1:4:4, 1:5:4, 2:1:4, 2:2:4, 2:3:4, 2:4:4, 2:5:4, 3:1:4, 3:2:4, 3:3:4, 3:4:4, 3:5:4, 4:1:4, 4:2:4, 4:3:4, 4:4:4, 4:5:4, 5:1:4, 5:2:4, 5:3:4, 5:4:4 or 5:5:4. In certain embodiments of the formulations described herein the ratio by weight of the water soluble surfactant, a non-ionic surfactant and a water insoluble surfactant 20 is about 1:1:5, 1:2:5, 1:3:5, 1:4:5, 1:5:5, 2:1:5, 2:2:5, 2:3:5, 2:4:5, 2:5:5, 3:1:5, 3:2:5, 3:3:5, 3:4:5, 3:5:5, 4:1:5, 4:2:5, 4:3:5, 4:4:5, 4:5:5, 5:1:5, 5:2:5, 5:3:5, 5:4:5 or 5:5:5. In certain 25 embodiments the ratio of by weight of the water soluble surfactant, a non-ionic surfactant and a water insoluble surfactant is 1:3:5.

In the formulations described herein, at least one of the surfactants is a water soluble surfactant. Suitable water soluble surfactants include, but are not limited to, polyethylene glycol sorbitan fatty acid esters and hydrophilic transesterification products of a polyol with at least one member of the group from triglycerides; vegetable oils and hydrogenated vegetable oils such as glycerol, ethylene glycol, polyethylene glycol, sorbitol, propylene glycol, pentaerythritol, or a saccharide, d-alpha-tocopheryl polyethylene glycol 1000 succinate. In certain embodiments of 30 the formulations described herein, the water soluble surfactant is propylene glycol.

In the formulations described herein, at least one of the surfactants is a non-ionic surfactant. Suitable non-ionic surfactants include, but are not limited to, ethylene glycol monostearate, propylene glycol myristate, glyceryl monostearate, glyceryl stearate, polyglyceryl-4-oleate, sorbitan acylate, sucrose acylate, PEG-150 laurate, PEG-400 monolaurate, 35 polyoxyethylene monolaurate, polysorbates including TWEEN 80, polyoxyethylene octylphenylether, PEG-1000 cetyl ether, polyoxyethylene tridecyl ether, polypropylene glycol butyl ether, POLOXAMER 401, pluronic, stearoyl monoisopropanolamide, CREMOPHOR EL (polyethoxylated castor oil), SPAN 80 (sorbitan oleate), and polyoxyethylene hydrogenated

tallow amide. In certain embodiments of the formulations described herein, the nonionic surfactant is SPAN 80, TWEEN 80 or CREMOPHOR EL. In certain embodiments, of the formulations described herein the non-ionic surfactant is CREMOPHOR EL.

5 In the formulations described herein, at least one of the surfactants is a water insoluble surfactant. Suitable water insoluble surfactants include, but are not limited to, CAPRYOL 90 (propylene glycol monocaprylate), LAUROGLYCOL FFC (propylene glycol monolaurate), Propymuls (propylene glycol ricinoleate), Myverol P-06 (propylene glycol monooleate), CAPTEX 200 (propylene glycol dicaprylate/dicaprate) and CAPTEX 800 (propylene glycol dioctanoate). In certain embodiments of the formulations described herein, the water insoluble surfactant is selected from the group consisting of LAUROGLYCOL FFC and CAPRYOL 90. In certain embodiments the water insoluble surfactant is LAUROGLYCOL FFC. 10 In certain embodiments the water insoluble surfactant is CAPRYOL 90.

15 In certain embodiments, the formulations described herein contain a digestible long-chain fatty acid ester. Suitable digestible long-chain fatty acid esters include, but are not limited to, glycerine trioleate and ethyl oleate. In certain embodiments, the digestible long-chain fatty acid ester is ethyl oleate.

20 In the formulations described herein, the long-chain fatty acid ester is present in the amount of 1% to 10% by weight. In certain embodiments, the long-chain fatty acid ester is present in the amount of 7% by weight. In certain embodiments, the long-chain fatty acid ester is present in the amount of 5% by weight. In other embodiments, the long-chain fatty acid ester is present in the amount of 3% by weight.

Certain embodiments of the formulations described herein may include a cosolvent such as TRANSCUTOL P (2-(2-ethoxyethoxy)ethanol).

25 Also described herein are methods for the treatment of hypogonadism comprising administering to a patient in need thereof a pharmaceutical formulations as described herein. Also described herein are uses of the formulations described herein for the treatment of hypogonadism or the manufacture of a treatment of hypogonadism.

EXAMPLES

30 Solubility of Testosterone Undecanoate

Solubility experiments were conducted on certain SNEDDS as well as on the individual components used in the SNEDDS. Solubility experiments were conducted on 250 μ l scale and started with 25mg testosterone undecanoate. Room temperature solid fats and most mixtures containing room temperature solid fats were stirred overnight at 40°C. All other excipients (oils, surfactants and mixtures hereof) were stirred overnight at room temperature. If visual check showed complete dissolution of testosterone undecanoate, another 25mg of testosterone undecanoate was added and stirred to equilibrium. This step was repeated until the point of saturation was passed. The resulting suspensions were centrifuged for 6 minutes at

14.000rpm. The supernatant was pipetted carefully from the vial and checked for visual clarity before dilution 200 to 1000 times with H₂O/THF (1/9 v/v). Concentration of testosterone undecanoate in the solutions was measured with HPLC. Table 1 shows the results.

5 Table 1

Excipients and SNEDDS mixtures	Solubility (mg/ml)
Surfactants - cosolvents	
PROPYLENE GLYCOL	2.1
CREMOPHOR EL	27.2
POLYSORBATE 80 (TWEEN80)	28.4
TRANSCUTOL P	57.2
Non-ionic or water insoluble surfactants - cosolvent	
SPAN 80	130.4
LAUROGLYCOL FFC	175.7
CAPRYOL 90	226.7
Digestible long-chain fatty acid esters	
Glycerine trioleate	60.9
Ethyl oleate	117.3
Digestible oils containing long-chain fatty acids	
Sunflower Seed Oil	67.3
Corn Oil	72.1
Peanut Oil	73.3
Non-digestible oils	
Castor Oil	103.1
Non-emulsifying and non-digestible formulation	
ANDRIOL TESTOCAPSS formulation (Castor Oil/LAUROGLYCOL FFC (6/4))	136.5
SNEDDS – undigestible formulations	
Formulation A (CAPRYOL 90/ TWEEN 80/ TRANSCUTOL P (2:5:5))	56.7
Formulation B (Propylene glycol/CREMOPHOR EL/CAPRYOL 90 (1:3:5))	104.7
SNEDDS formulations with digestible component	
Formulation C (Sunflower Seed Oil/CREMOPHOR EL/SPAN	57.5

80 (3/4/3 w/w/w))	
Formulation D (Corn Oil/CREMOPHOR EL/SPAN 80 (3/4/3 w/w/w))	58.9
Formulation E (Sunflower Seed Oil/ CREMOPHOR EL/ Maisine (1:1:1))	66.0

As you can see Formulation B is the closest to the ANDRIOL TESTOCAPS formulation for solubilizing testosterone undecanoate.

5 Homogeneity of Formulations

The formulations containing testosterone undecanoate should stay clear and homogeneous. For this purpose testosterone undecanoate has been dissolved in selected formulations. The amount of testosterone undecanoate added to the SNEDDS depends on the maximum solubility. To test the stability of the formulations in terms of homogeneity during storage, 1ml of each of the formulations listed in Table 2 was put into a glass vial, closed under N₂ and kept at room temperature for 4 weeks. After 4 weeks the visual appearance was noted. All tested formulations stayed homogeneous upon visual inspection after 4 weeks. In two formulations, Formulation C and Formulation G some glass-like crystals appeared within 4 weeks. These crystals were crystallized testosterone undecanoate, indicating the amount of dissolved testosterone undecanoate was close to the maximum solubility.

Table 2

Formulation	Amount of Testosterone Undecanoate (%)	> 4 weeks standing at room temperature
Formulation B	9	Clear
Formulation C	6	Some glass-like crystals on bottom
Formulation D	6	Clear
Formulation F (Propylene glycol/Cremophor RH40/Capryol 90 (1:3:5))	9	Clear
Formulation G (Formulation B + 5% EtOH (w/w))	12	Some glass-like crystals on bottom
Formulation H	12	Clear

(Formulation B + 5% ethyl oleate (w/w)		
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Emulsification of Formulations

For determination of the self-emulsifying properties of the selected formulations in watery systems, two methods were used. The first method was slow titration of the oily mixture with aqueous (Method 1). The second method was addition of the oily mixture to the aqueous phase (Method 2).

Method 1: Slow titration of oily mixture with aqueous phase. Water was added in portions to 250 μ l SNEDDS in a glass vial with a magnetic stirrer bar, starting with 50 μ l portions and ending with a 10ml portion. After addition of each portion the mixture was stirred until no more changes in constitution were seen. The constitution was noted and another portion of water was added. These steps were repeated to a volume of 15ml. Then 1ml was taken and added to 4ml of stirring water. The resulting solution was stirred at least 2h before visual appearance was noted.

Method 2: Addition of oily mixture to aqueous phase. 25 μ l SNEDDS was added to 6.25ml stirred water. If the emulsion was not formed within one minute vortexing was used to mix the two phases. After mixing the solution was stirred for at least 2h before the visual appearance was noted and/or the droplet size was measured.

Dilution of both methods was chosen to lead to a concentration of approx. 1ml SNEDDS in 250ml water, the amount of water stands for the stomach-volume. Several SNEDDS were emulgated via Method 1 as well as Method 2 to compare the resulting emulsions. The formulations which are emulgated contain 6%, 9% or 12% testosterone undecanoate. This depends on the maximum solubility. 12% matches the testosterone undecanoate concentration in ANDRIOL TESTOCAPSS.

To score the self-emulsifying properties of the formulations, the visual appearance of the emulsions were noted in Table 3. A milky appearance of the emulsion indicated a larger droplet size; a slightly milky, milky haze, haze, bluish transparent or clear appearance indicates possible formation of a nano-emulsion. Droplet size parameters of the emulsions in the range of slightly milky to clear are measured with Dynamic Light Scattering techniques.

Table 3

Formulation	Amount of Testosterone	Method	Visual appearance after 16hrs of stirring
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	Undecanoate (%)		
Formulation B	9	1	Haze
Formulation C	6	1	Bluish transparent
Formulation D	6	1	Bluish transparent
Formulation F (Propylene glycol/Cremophor RH40/Capryol 90 (1:3:5))	9	1	Light milky
Formulation G (Formulation B + 5% EtOH (w/w))	12	2	Haze
Formulation H (Formulation B + 5% ethyl oleate (w/w))	12	2	Milky haze

Droplet Size Measurements

5 Droplet sizes were obtained with Dynamic Light Scattering (DLS) techniques. These measurements were performed to get more insight in the droplet size and droplet size distribution of the droplets in the emulsions obtained via Method 1 or 2. Measurements were performed with a Malvern DLS Nanosizer or Zetasizer Nano ZS. Approximately 1ml of the emulsion was pipetted into a low volume disposable sizing cuvette, checked for absence of air-bubbles and placed in the cuvet holder. Results are shown in Table 4.

10 Table 4

Formulation	Amount of Testosterone Undecanoate (%)	Method	Total Average diameter (nm)	PdI (polydispersity index)	Average diameter peak 1 (nm)	Volume Peak 1 (%)
Formulation B	9	1	68.5	0.15	54.6	100
Formulation C	6	1	41.5	0.4	20.4	100
Formulation D	6	1	27.9	0.21	16.9	100
Formulation F (Propylene glycol/Cremophor RH40/Capryol 90 (1:3:5))	9	1	142.1	0.14	154.6	100
Formulation G	12	2	55.7	0.18	44.0	99

(Formulation B + 5% EtOH (w/w)						
Formulation H (Formulation B + 5% ethyl oleate (w/w)	12	2	69.6	0.22	56.0	97

Animal Study

Formulations Used in Animal Studies

5 Capsules were made with the formulations shown in Table 5. The liquid excipients were weighed and mixed. Subsequently, the testosterone undecanoate was added, and the mixtures were placed on a rollerbank for a period between 1 and 3 days. Table 6 shows the amount of formulation and testosterone undecanoate per capsule.

10 Table 5

Formulation	Testosterone Undecanoate (%)	Propylene glycol (mg)	Cremophor EL (mg)	Capryol 90 (mg)	5% ethyl oleate	Testosterone Undecanoate (mg)	Total
Formulation B0	0	116.5	354.1	529.5	-	-	1000
Formulation B	9	106.0	322.2	481.8	-	90.0	1000
Formulation B1	7.5	107.7	327.5	489.7	-	75.0	1000
Formulation H0	0	110.6	336.4	503.0	50.0	-	1000
Formulation H1	9	100.7	306.1	457.7	45.5	90.0	1000
Formulation H2	7.5	102.3	311.2	465.3	46.3	75.0	1000

Table 6

Formulation	Testosterone Undecanoate (%)	Amount of Mixture per capsule (mg)	Amount of Testosterone Undecanoate per capsule (mg)
Formulation B0	0	444.44	0

Formulation B	9	444.44	40
Formulation B1	7.5	533.33	40
Formulation H0	0	444.44	0
Formulation H1	9	444.44	40
Formulation H2	7.5	533.33	40

To estimate the emulsification behavior of the formulations in the gastro-intestinal (GI) tract, the capsules in Table 6 were diluted with different amounts of water or Simulated Gastric Fluid (SGF). A single capsule was added to a volume of 250, 60, or 30 mL to mimic a range of gastric volumes in man and dog. Visual appearance and droplet sizes were determined. For all formulations a bluish transparent emulsion was observed for capsules added to 250mL of liquid. For all formulations a bluish transparent emulsion with a slight white haze was observed for capsules added to 60mL of liquid. For all formulations a milky white haze was observed for capsules added to 30mL of liquid. Droplet size of the nano-emulsions were also measured and shown below in Table 7.

After 6 weeks of storage at 5°C/ambient humidity, 25°C/60%RH or 40°C/75%RH the emulsions in 60 mL of SGF had a bluish white haze. Droplet size of emulsions made from capsules that were stored for 6 weeks at different conditions are shown in Table 8.

15 Table 7

		Volume peak 1 (and 2 in parentheses) in d.nm						
		250 mL		60mL		30mL		
Formulation	TU	Water	118.6	86.1	49.5	51.0	56.5	48.6
Formulation B0	(0% TU)	Water	118.6	86.1	49.5	51.0	56.5	(201.2)
		SGF	92.7 (303.0)	93.4 (334.7)	53.7	55.5	67.4 (348.2)	69.7 (357.2)
Formulation B	(9% TU)	Water	80.4	n.d.	52.2	n.d.	62.9	n.d.
		SGF	96.5	n.d.	64.0	n.d.	204.5 (49.2)	n.d.
Formulation B1	(7.5% TU)	Water	94.9	100.3	63.4	57.0	156.5 (1331.0)	68.4
		SGF	146.5	212.6	97.7	75.4	240.8	234.0 (58.3)
Formulation		Water	69.9	102.5	50.1	51.6	64.3	56.8

H0 (0% TU)							
	SGF	133.5	86.8 (207.9)	53.6	54.6	71.1	57.1 (283.7)
Formulation H1 (9% TU)	Water	64.2	n.d.	59.2	n.d.	82.2	n.d.
	SGF	82.1	n.d.	63.7	n.d.	126.6	n.d.
Formulation H2 (7.5% TU)	Water	78.3	89.3	63.2	57.6	113.0	67.6
	SGF	99.0	105.8	67.3	67.7	69.5 (223.8)	187.3 (51.5)

All formulations form the best emulsion when emulsified in 60 mL water or SGF. Little variability is observed between water and SGF. All formulations seem to emulsify equally well in 60 mL of medium. For 250 and 30 mL, the emulsions seem coarser, and sometimes more than one peak is observed. For these volumes, the results are better in water than in SGF. The formulations comprising ethyl oleate seem to form a better emulsion in these volumes than the formulations without ethyl oleate. Considering that the 1/60 dilution is used to predict the in-vivo behavior in fasted state man since this mimics the ratio in human fasted state stomach, it is expected that all formulations form nanoemulsions in the fasted human gastro-intestinal tract.

10

Table 8

Formulation	Volume peak 1 (and 2 in parentheses) in d.nm			
	T=0 (emulsions in 250 mL water)	T=6 weeks (emulsion in 60mL SGF)	5°C/amb	25°C/60%RH
Formulaton B0 (0% TU)	37.0	54.1	53.4	55.3
Formulaton B (9% TU)	55.6	75.9	73.0 (703.7 (8%))	70.8
Formulaton B1 (7.5% TU)	56.4	64.6	64.4	65.0
Formulaton H0 (0% TU)	44.1	54.7	65.1	54.5
Formulaton H (9% TU)	55.0	67.7	67.9	67.3

Formulaton H1 (7.5% TU)	39.3	64.3	64.7	63.9
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For almost all formulations and all conditions, nanoemulsions were formed. (<100nm). No large difference was observed between the different storage temperatures, indicating that the same droplet sizes can be obtained after storage.

5 Crystallization tendency was also measured in the capsule formulations. All formulations remained clear at 3 hours and 96 hours when stored at 7°C. Formulations were also exposed to a freeze-thaw cycle of 3 hours at -80°C, then 1 hour at room temperature, then 96 hours at -80°C and finally 2 hours at room temperature. All formulations except Formulation B were solid at -80°C and clear at room temperature. Formulation B was clear at room
10 temperature with some tiny needles present but after shaking was clear within a few hours.

15 Degradation products of the capsules were determined directly after manufacturing of the capsules and after storage during six weeks at 5°C/ambient humidity, 25°C/60%RH, and 40°C/75%RH. The results show that the stability of the different formulations was similar. Some degradation products were formed after storage at 40°C/75%RH during six weeks and the above formulations are expected to have a shelf-life of about 9 months at 2-25°C.

In vivo Study

20 An *in vivo* study was performed. Twelve female Beagle dogs with body weight range 7.44-12.9 kg, aged 1-2 years at dosing were assigned to three different dosing groups and administered test formulations according to the scheme shown in Table 5.

Table 5

Week	Group No.	Pre-Dose Fast/Fed	Dose of Testosterone Undecanoate	Formulation
1	1	Fasted	40mg	Formula B with 9% Testosterone Undecanoate
	2	Fed	40mg	Formula H with 9% Testosterone Undecanoate
	3	Fasted	40mg	ANDRIOL TESTOCAPSS
2	1	Fed	40mg	Formula B with 9% Testosterone Undecanoate
	2	Fasted	40mg	Formula H with 9% Testosterone Undecanoate
	3	Fed	40mg	ANDRIOL TESTOCAPSS

3	1	Fasted	40mg	Formula B with 9% Testosterone Undecanoate
	2	Fed	40mg	Formula H with 9% Testosterone Undecanoate
	3	Fasted	40mg	ANDRIOL TESTOCAPSS

For testosterone, the mean AUC_{0-12hr} were 23.5 and 33.8 nM*hr for Formula B and Formula H, respectively, in fasted dogs compared to 9.57 nM*hr for ANDRIOL TESTOCAPS. The mean AUC_{0-12hr} increased to 90.8 and 123 nM*hr for Formula B and Formula H, respectively, in dogs when dosing with high fat meal compared to 50.6 nM*hr for ANDRIOL TESTOCAPS. The mean C_{max} were 11.9 and 18.5 nM for Formula B and Formula H, respectively, in fasted dogs compared to 4.89 nM for ANDRIOL TESTOCAPS. The mean C_{max} increased to 42.3 and 57.9 nM for Formula B and Formula H, respectively, in dogs when dosing with high fat meal compared to 18.2 nM for ANDRIOL TESTOCAPS. In addition, the median T_{max} increased from 1.5, 1.2, 2.2 hr in fasted state to 3.0, 3.0 and 4.0 hr for Formula B, Formula H and ANDRIOL TESTOCAPS, respectively, when dosing with high fat meal.

For testosterone undecanoate (TU), the mean AUC_{0-12hr} were 205 and 423 nM*hr for Formula B and Formula H, respectively, in fasted dogs compared to 89.1 nM*hr for ANDRIOL TESTOCAPS. The mean AUC_{0-12hr} increased to 1660 and 2300 nM*hr for Formula B and Formula H, respectively, in dogs when dosing with high fat meal compared to 1130 nM*hr for ANDRIOL TESTOCAPS. The mean C_{max} were 144 and 311 nM for Formula B and Formula H, respectively, in fasted dogs compared to 55.6 nM for ANDRIOL TESTOCAPS. The mean C_{max} increased to 1090 and 1550 nM for Formula B and Formula H, respectively, in dogs when dosing with high fat meal compared to 512 nM for ANDRIOL TESTOCAPS. In addition, the median T_{max} slightly increased from 1.5, 1.5, 2.5 hr in fasted state to 2.5, 2.5 and 3.0 hr for Formula B, Formula H and ANDRIOL TESTOCAPS, respectively, when dosing with high fat meal.

The AUC_{0-12hr} ratios of testosterone for tested formulations in fed versus fasted state were 3.86, 3.64 and 5.29 for Formula B, Formula H and ANDRIOL TESTOCAPS, respectively. The AUC_{0-12hr} ratios of testosterone undecanoate for tested formulations in fed versus fasted state were 8.10, 5.44 and 12.7 for Formula B, Formula H and ANDRIOL TESTOCAPS, respectively. Although significant food effect would still be expected for tested formulations, the tested formulations showed decreased exposure ratio between fed and fasted state than ANDRIOL TESTOCAPS.

When looking into the AUC_{0-12hr} ratios of testosterone for tested formulation versus ANDRIOL TESTOCAPS in fed state, the AUC_{0-12hr} ratios of testosterone for tested formulations versus ANDRIOL TESTOCAPS when dosing with high fat meal were 1.79 and 2.43 for Formula B and Formula H, respectively. While in fasted state, the increase of exposure

extended to 2.46-fold and 3.53-fold for Formula B and Formula H, respectively. For testosterone undecanoate, the AUC_{0-12hr} ratios for tested formulations versus ANDRIOL TESTOCAPS when dosing with high fat meal were 1.47 and 2.04 for Formula B and Formula H, respectively. While in fasted state, the increase of exposure extended to 2.30-fold and 4.75-fold for Formula B and

5 Formula H, respectively.

In summary, based on the results of this dog study, food effect is still observed for tested formulations. However, the tested formulations showed significant increase of exposure than the ANDRIOL TESTOCAPS (average ~2x in fed state and ~3.5x in fasted state for testosterone undecanoate). A decreased exposure ratio between fed and fasted state than

10 ANDRIOL TESTOCAPS was observed for tested formulations.

WHAT IS CLAIMED IS:

1. A pharmaceutical formulation comprising:
testosterone undecanoate;
5 a water soluble surfactant, a non-ionic surfactant and a water insoluble surfactant; and
a digestible long-chain fatty acid ester.
2. The pharmaceutical formulation of claim 1, wherein the water soluble surfactant, a non-ionic surfactant and a water insoluble surfactant are present in a weight ratio of 1:3:5.
- 10 3. The pharmaceutical formulation of claim 1, wherein the water soluble surfactant is selected from the group consisting of glycerol, ethylene glycol, polyethylene glycol, sorbitol and propylene glycol.
- 15 4. The pharmaceutical formulation of claim 1, wherein the water soluble surfactant is propylene glycol.
5. The pharmaceutical formulation of claim 1, wherein the water insoluble surfactant is selected from the group consisting of propylene glycol monocaprylate, propylene glycol monolaurate, propylene glycol ricinoleate, propylene glycol monooleate, propylene glycol dicaprylate/dicaprate and propylene glycol dioctanoate).
- 20 6. The pharmaceutical formulation of claim 1, wherein the water insoluble surfactant is propylene glycol monocaprylate.
- 25 7. The pharmaceutical formulation of claim 1, wherein the non-ionic surfactant is selected from the group consisting of sorbitane monooleate, polysorbate 80 and polyethoxylated castor oil.
- 30 8. The pharmaceutical formulation of claim 1, wherein the non-ionic surfactant is polyethoxylated castor oil.
9. The pharmaceutical formulation of claim 1, wherein the digestible long-chain fatty acid ester is selected from the group consisting of glycerine trioleate and ethyl oleate.

10. The pharmaceutical formulation of claim 1, wherein the digestible long-chain fatty acid ester is ethyl oleate.

11. The pharmaceutical formulation of claim 1, wherein the amount of the digestible long-
5 chain fatty acid ester is about 5% by weight.

12. The pharmaceutical formulation of claim 1, wherein the amount of testosterone undecanoate is about 6% to 12% by weight.

10 13. The pharmaceutical formulation of claim 1, wherein the amount of testosterone undecanoate is less than 10% by weight.

14. The use of the formulation of claim 1 for the treatment of hypogonadism.

15 15. A pharmaceutical formulation consisting essentially of:
testosterone undecanoate;
a water soluble surfactant, a water insoluble surfactant and a non-ionic surfactant; and
a digestible long-chain fatty acid ester.