FORM 2

THE PATENTS ACT 1970

(39 of 1970)

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The Patents Rules, 2003

COMPLETE SPECIFICATION

(See section 10 and rule 13)

1. TITLE OF THE INVENTION

A PARENTERAL PHARMACEUTICAL COMPOSITION OF DYDROGESTERONE

2. APPLICANTS

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3. PREAMBLE TO THE DESCRIPTION

Complete

The following specification describes the invention and the manner in which it is to be performed.

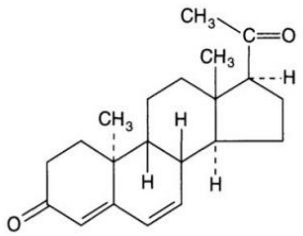
A PARENTERAL PHARMACEUTICAL COMPOSITION OF DYDROGESTERONE

FIELD OF THE INVENTION

The present invention relates to a parenteral pharmaceutical composition comprising therapeutically effective amount of dydrogesterone, and one or more pharmaceutically acceptable excipients. Further, the present invention also relates to the process of preparation of the parenteral pharmaceutical composition thereof.

BACKGROUND OF THE INVENTION

Dydrogesterone, also known as 6-dehydro-9β, 10α-progesterone or as 9β, 10α-pregna-4,6-diene-3,20-dione, is a synthetic pregnane steroid and a derivative of progesterone and retroprogesterone (9β,10α-progesterone) having formula I.



Dydrogesterone

Dydrogesterone is a progestin medication which is used for treatment of irregular duration of cycles and irregular occurrence and duration of periods caused by progesterone deficiency. Further, combined with an estrogenic substance, dydrogesterone can be applied in secondary amenorrhoea, dysfunctional uterine bleeding and post-menopausal complaints where endogenous progesterone deficiency is implicated.

There are several references known in the literature, which describe the different composition of dydrogesterone, which are used in the treatment of various diseases.

U.S. Patent No. 7,683,047 discloses a method of treating endometrial hyperplasia in a subject, said method comprising: administering continuously and uninterruptedly for a

first predetermined time period a first dose of a progestin agent to said subject; and administering continuously and uninterruptedly for a second predetermined time period a second dose of a progestin agent to said subject.

U.S. Patent Publication No. 20050020553 A discloses a method of inhibiting spontaneous or habitual miscarriage, said method comprising administering to a female patient in need of such treatment an effective amount of at least one non-endogenous gestagen compound from the moment of ovulation on.

U.S. Patent Publication No. 20110152840 A1 discloses a method for reducing the occurrence of preterm delivery, the method comprising: administering an oral pharmaceutical composition comprising a steroid hormone to a pregnant female subject having no history of preterm delivery and exhibiting one or more risk factors for preterm delivery.

U.S. Patent Publication No. 20040202713 A1 disclose a contraceptive method comprising sequentially administering a plurality of dosage units containing a hormone composition to a female of childbearing capability so as to provide the hormone composition in an amount which is effective to inhibit ovulation, wherein the hormone composition is dydrogesterone component or a combination of estrogen and dydrogesterone component.

PCT Patent Publication No. 2012055840 A1 disclose an oral pharmaceutical composition comprising a hormonal agent, a biocompatible zinc salt, and pharmaceutical acceptable excipients.

PCT Patent Publication No. 2004019954 A1 disclose an improved oral pharmaceutical preparation, for administration to a female in need of estrogen replacement, comprising a plurality of doses arranged in alternating standard dose estrogen phases and ultra-low dose estrogen phases.

Dydrogesterone is also known for the treatment of progesterone deficiency such as treatment of threatened abortion and pre-eclampsia. Threatened abortion is defined as pregnancy-related bloody vaginal discharge or frank bleeding during the first half of

pregnancy without cervical dilatation. Nearly 25 percent of pregnant women have some degree of vaginal bleeding during the first two trimesters and about 50 percent of these progress to an actual abortion. It is associated with an increased risk of poor obstetric outcomes such as preterm labour, low birth weight, and premature rupture of membranes. Dydrogesterone has consistently proved to be more effective than standard supportive care or placebo, and demonstrated a positive trend towards being more effective than vaginal micronized progesterone in the management of threatened miscarriage. Dydrogesterone helps in relieving lower back pain, abdominal pain, and haemostasis in the threatened abortion, Female infertility, Pain during menstruation, Premenstrual syndrome (PMS), Endometriosis, Heavy menstrual bleeding, pre-eclampsia.

The aforementioned publications disclose or suggest solid oral formulations of dydrogesterone. However, because of the slow gastrointestinal absorption and high hepatic metabolism of dydrogesterone, achieving the desired plasma levels is often difficult or delayed with oral administration. Attempts have been made to provide optimal, stable parenteral pharmaceutical compositions of dydrogesterone, however, because of the lipophilicity and low aqueous solubility of dydrogesterone, there is currently no commercially available formulation of dydrogesterone for parenteral administration.

Therefore, there is a strong need felt in the art for parenteral pharmaceutical compositions of dydrogesterone. After extensive experimentation and lots of efforts, the inventors have developed a parenteral pharmaceutical composition of dydrogesterone which is optimal, stable, and patient compliant with less to no irritation or pain at the site of injection.

OBJECTIVES OF THE PRESENT INVENTION

The principal objective of the present invention is to provide a parenteral pharmaceutical composition comprising dydrogesterone and one or more pharmaceutically acceptable excipients.

Another objective of the present invention is to provide a process for the preparation of

a parenteral pharmaceutical composition comprising dydrogesterone and one or more pharmaceutically acceptable excipients.

Another objective of the present invention is to provide a ready to use parenteral pharmaceutical composition comprising dydrogesterone and one or more pharmaceutically acceptable excipients.

Another objective of the present invention is to provide a parenteral pharmaceutical composition comprising dydrogesterone, wherein the composition is a concentrate for dilution before administration.

Another objective of the present invention is to provide a parenteral pharmaceutical composition comprising dydrogesterone and one or more pharmaceutically acceptable excipients, wherein the pharmaceutically acceptable excipient is selected from the group comprising solubilizing agent(s), buffering agent(s), antioxidant(s), chelating agent(s), carrier(s), preservative(s), tonicity agent(s), pH adjusting agent(s) and/or combinations thereof.

SUMMARY OF THE INVENTION

The present invention provides a parenteral pharmaceutical composition comprising therapeutically effective amount of dydrogesterone and one or more pharmaceutically acceptable excipients.

According to one aspect, the present invention provides a parenteral pharmaceutical composition comprising therapeutically effective amount of about 0.1% w/v to about 10% w/v of dydrogesterone, about 0.01% w/v to about 80 % w/v of solubilizing agent(s) and one or more pharmaceutically acceptable excipients.

Another objective of the present invention is to provide a parenteral pharmaceutical composition comprising therapeutically effective amount of about 0.1% w/v to about 10% w/v of dydrogesterone, one or more carrier(s) and one or more pharmaceutically acceptable excipients.

According to another aspect, the present invention provides a sustained release parenteral pharmaceutical composition comprising therapeutically effective amount of about 0.1% w/v to about 10% w/v of dydrogesterone, one or more carrier(s), and one or more pharmaceutically acceptable excipients.

According to another aspect, the present invention provides a parenteral pharmaceutical composition comprising dydrogesterone and one or more pharmaceutically acceptable excipients, wherein the composition is having a pH in a range of 2 to 11.

According to another aspect, the present invention provides a parenteral pharmaceutical composition comprising therapeutically effective amount of about 0.1% w/v to about 10% w/v of dydrogesterone, and one or more pharmaceutically acceptable excipients, wherein the one or more pharmaceutically acceptable excipients is selected from the group comprising solubilizing agent(s), buffering agent(s), antioxidant(s), chelating agent(s), carrier(s), preservative(s), tonicity agent(s), pH adjusting agent(s) and/or combinations thereof.

According to another aspect, the present invention provides a parenteral pharmaceutical composition comprising therapeutically effective amount of about 0.1% w/v to about 10% w/v of dydrogesterone, about 0.01% w/v to about 80 % w/v of solubilizing agent(s), one or more carrier(s), and one or more pharmaceutically acceptable excipients.

According to another aspect, the present invention provides a parenteral pharmaceutical composition comprising about 1 mg to about 50 mg of dydrogesterone, about 0.01% w/v to about 80 % w/v of solubilizing agent(s), one or more carrier(s), and one or more pharmaceutically acceptable excipients, wherein the one or more pharmaceutically acceptable excipients is selected from the group comprising:

(a) buffering agent(s) in an amount of about 0.01% w/v to about 20 % w/v,
(b) preservative(s) in an amount of about 0.001% w/v to about 20% w/v,
(c) tonicity agent(s) in an amount of about 0.01% w/v to about 10% w/v,
(d) chelating agent(s) in an amount of about 0.001% w/v to about 10% w/v,
(e) antioxidant(s) in an amount of about 0.001% w/v to about 10% w/v, of the pharmaceutical composition.

According to another aspect, the present invention provides a parenteral pharmaceutical composition comprising about 1 mg to about 50 mg of dydrogesterone, about 0.01% w/v to about 90 % w/v of one or more carrier(s), and one or more pharmaceutically acceptable excipients, wherein the one or more pharmaceutically acceptable excipients is selected from the group comprising:

(a) buffering agent(s) in an amount of about 0.01% w/v to about 20 % w/v,
(b) preservative(s) in an amount of about 0.001% w/v to about 20% w/v,
(c) tonicity agent(s) in an amount of about 0.01% w/v to about 10% w/v,
(d) chelating agent(s) in an amount of about 0.001% w/v to about 10% w/v,
(e) antioxidant(s) in an amount of about 0.001% w/v to about 10% w/v, of the pharmaceutical composition.

According to another aspect, the present invention provides a parenteral pharmaceutical composition comprising dydrogesterone and one or more pharmaceutically acceptable excipients, wherein the parenteral pharmaceutical composition can be aqueous or non-aqueous or hydroalcoholic composition.

According to another aspect, the present invention provides a parenteral pharmaceutical composition comprising about 1 mg to about 50 mg of dydrogesterone, Hydroxypropyl-β-cyclodextrin, one or more pharmaceutically acceptable excipients, and water; wherein dydrogesterone and Hydroxypropyl-β-cyclodextrin are present in a molar ratio of about 1:1 to about 1:20.

According to another aspect, the present invention provides a parenteral pharmaceutical composition comprising about 1 mg to about 50 mg of dydrogesterone, one or more carrier(s) and one or more pharmaceutically acceptable excipients; wherein dydrogesterone and one or more carrier(s) are present in a molar ratio of about 1:1 to about 1:60.

According to another aspect, the present invention provides a parenteral pharmaceutical composition comprising about 1 mg to about 50 mg of dydrogesterone, one or more carrier(s) and one or more pharmaceutically acceptable excipients; wherein dydrogesterone and one or more carrier(s) are present in a molar ratio of about 1:1 to about 1:80.

According to another aspect, the present invention provides a parenteral pharmaceutical composition comprising about 1 mg to about 50 mg of dydrogesterone, Hydroxypropyl-β –cyclodextrin, ethanol, and one or more pharmaceutically acceptable excipients, wherein the one or more pharmaceutically acceptable excipients is selected from the group comprising:

(a) buffering agent(s) in an amount of about 0.01% w/v to about 20 % w/v,
(b) preservative(s) in an amount of about 0.001% w/v to about 20% w/v,
(c) tonicity agent(s) in an amount of about 0.01% w/v to about 10% w/v,
(d) chelating agent(s) in an amount of about 0.001% w/v to about 10% w/v,
(e) antioxidant(s) in an amount of about 0.001% w/v to about 10% w/v, of the pharmaceutical composition.

According to another aspect, the present invention provides a parenteral pharmaceutical composition comprising dydrogesterone and one or more pharmaceutically acceptable excipients, wherein the pharmaceutical composition filled in suitable container, wherein the suitable container includes vial(s), prefilled syringe(s), ampoule(s), cartridge(s), auto-injector, bottle(s) and/or bag(s).

According to another aspect, the present invention provides a process for preparation of a parenteral pharmaceutical composition comprising dydrogesterone and one or more pharmaceutically acceptable excipients, wherein said process comprises:

(a) water is collected in a suitable vessel;
(b) carrier(s), solubilizing agent(s), and therapeutically effective amount of dydrogesterone are added simultaneously or one after the other to step (a) to obtain a clear solution;
(c) optionally, one or more other pharmaceutically acceptable excipients was added to the solution of step (b);
(d) optionally, pH of the solution of step (b) or (c) was adjusted;
(e) volume of the solution of step (b) was makeup or pH adjusted solution of step (d) to 100% batch size with water; and
(f) solution of step (e) was filtered and then filled the solution in suitable container.

According to another aspect, the present invention provides a parenteral pharmaceutical composition comprising dydrogesterone, and one or more pharmaceutically acceptable excipients, wherein the pharmaceutical composition provides extended or sustained or slow absorption of drug after administration or from the site of administration.

According to another aspect, the present invention provides a parenteral pharmaceutical composition comprising dydrogesterone, and one or more pharmaceutically acceptable excipients, wherein the pharmaceutical composition provides immediate absorption of drug after administration or from the site of administration.

According to another aspect, the present invention provides a parenteral pharmaceutical composition comprising therapeutically effective amount of dydrogesterone and one or more pharmaceutically acceptable excipients; wherein the composition is administered for treatment of progesterone deficiency, threatened abortion, female infertility, pain during menstruation, premenstrual syndrome (PMS), endometriosis, heavy menstrual bleeding, and/or pre-eclampsia.

The details of one or more embodiments of the inventions are set forth in the description below. Other features, objects and advantages of the inventions will be apparent from the description.

DESCRIPTION OF THE INVENTION

The present invention provides a parenteral pharmaceutical composition comprising therapeutically effective amount of dydrogesterone and one or more pharmaceutically acceptable excipients.

Dydrogesterone is practically insoluble in water and freely soluble in organic solvent like chloroform. The oral bioavailability of dydrogesterone is very low, which is about 28% only. Due to the insolubility, the preparation of parenteral composition of dydrogesterone is very difficult.

Inventors of the present invention tried to formulate a parenteral composition of dydrogesterone. While working on parenteral composition of dydrogesterone, inventors

has observed that when dydrogesterone was mixed with the solvent or carrier, it results to obtained the turbid solution or solution with crystals or suspension. One requirement of the parenteral composition is that, it should be clear and should be free of particulate matter as per the requirement of regulatory agencies.

Inventors of the present invention has tried to solve this problem. Inventors has tried various excipients and combinations of excipient to solubilize the dydrogesterone. While working on the present invention, inventors have surprisingly found when dydrogesterone is mixed with one or more carrier(s) and one or more pharmaceutically acceptable excipients, it results to obtained a clear solution and no crystal structure or particulate matter in the solution is observed.

As used in this specification, the singular forms “a”, “an”, and “the” include plural references unless the context clearly dictates otherwise. Thus, for example, a reference to “a method” or “a process” includes one or more methods, one or more processes and/or steps of the type described herein and/or which will become apparent to those persons skilled in the art upon reading this disclosure and so forth.

As used herein the term “about” in reference to a numerical value means that variations of 10% above or below the numerical value are within the range described to the specified value.

The term “dydrogesterone” used in present invention refer to “dydrogesterone” or “dydrogesterone salt(s)” thereof. The suitable dydrogesterone salts includes inorganic acids such as hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid salt, carbonate salts; organic acids such as succinic acid, formic acids, acetic acid, diphenyl acetic acid, palmoic acid, triphenylacetic acid, caprylic acid, dichloroacetic acid, trifluoro acetic acid, propionic acid, butyric acid, lactic acid, citric acid, gluconic acid, mandelic acid, tartaric acid, malic acid, adipic acid, aspartic acid, fumaric acid, glutamic acid, maleic acid, malonic acid, benzoic acid, p-chlorobenzoic acid, dibenzoyl tartaric acid, oxalic acid, nicotinic acid, o-hydroxybenzoic acid, p-hydroxybenzoic acid, 1-hydroxy-naphthalene-2-carboxylic acid, hydroxynaphthalene-2-carboxylic acid, ethanesulfonic acid, ethane-1,2-disulfonic acid, 2-hydroxyethane sulfonic acid, methanesulfonic acid, (+)-camphor-10-sulfonic acid, benzenesulfonic acid,

naphthalene-2-sulfonic acid, p-toluenesulfonic acid and the like. The inorganic salts may further include alkali metal and alkaline earth metal salts such as sodium, potassium, barium, lithium, calcium, magnesium, rhodium, zinc, cesium, selenium, and the like.

The term "therapeutically effective amount" or "effective amount" used interchangeably, is defined to mean the amount or quantity of the active drug, which is sufficient to elicit an appreciable biological response when administered to the patient. It will be appreciated that the precise therapeutic dose will depend on the age and condition of the patient, the nature of the condition to be treated and will be at the ultimate discretion of the attendant physician.

The term "composition" or "pharmaceutical composition" or "parenteral pharmaceutical composition" or "dosage form" or "pharmaceutical formulation" or "formulation" as used herein synonymously include the pharmaceutical compositions in a form suitable for parenteral administration such as but not limited to sterile aqueous, hydro-alcoholic, or non-aqueous suspension, aqueous, hydro-alcoholic, or non-aqueous solution, or emulsion, liposomes, microparticles, or the like or any other suitable dosage form meant for parenteral administration. Further, parenteral pharmaceutical composition includes pharmaceutical composition for intramuscular, intravenous, sub-cutaneous, and intrathecal administration. In one embodiment, the pharmaceutical composition may be in the form of a unit dose composition or multi-dose composition.

The term 'extended or sustained or slow absorption' as used herein refers to absorption of drug over an extended period of time i.e. from about 2 hours to about 24 hours.

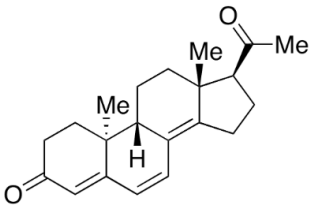
The term "pharmaceutically acceptable" refers to what is physiologically well tolerated by mammals or humans.

The term "excipient" or "pharmaceutically acceptable excipients" means a pharmacologically inactive component. As pharmaceutical excipients have various functions and contribute to the pharmaceutical composition in many different ways, e.g., solubilization, dilution, thickening, stabilization, and preservation. The properties that are commonly considered when formulating an active drug substance include bioavailability, ease of manufacture, ease of administration, and stability of the dosage

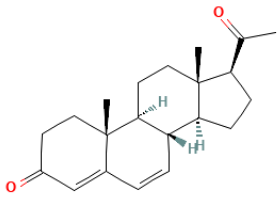
form. Due to the varying properties of the active drug substance to be formulated, dosage forms typically require pharmaceutical excipients that are uniquely tailored for the active drug substance in order to achieve advantageous physical and pharmaceutical properties.

The term “carrier(s)” or “pharmaceutically acceptable carrier(s)” is used interchangeably in the context of the present invention. “Carrier(s)” as used in the context of the present invention refer to purified water, water for injection, bacteriostatic water for injection, sterile water, isotonic saline water, buffered aqueous solution, ethanol, methanol, isopropyl alcohol, glycerin, propylene glycol, sesame oil, castor oil, arachis oil, mineral oil, sunflower oil, soybean oil, peppermint oil, corn oil, peanut oil, olive oil, cotton seed oil, hydrogenated vegetable oils, hydrogenated soybean oil, and medium-chain triglycerides of coconut oil, palm seed oil, polyethylene glycol (PEG), propylene glycol (PG), sorbitol, glycerine, acetone, benzyl alcohol, dimethyl sulfoxide, N-methyl-2-pyrrolidone, glycofurol, solketal, glycerol formal or combinations thereof.

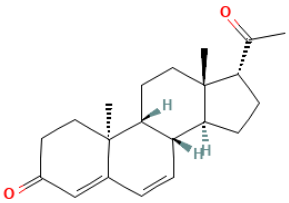
The term “impurity A” or “dydrogesterone impurity A” means an impurity with IUPAC name is 9β, 10α-pregna-4,6,8-(14)-triene-3, 20-dione. The structure is as follows:



The term “impurity B” or “dydrogesterone impurity B” means an impurity with IUPAC name is pregna-4,6-diene-3, 20-dione. The structure is as follows:



The term “impurity C” or “dydrogesterone impurity C” means an impurity with IUPAC name is 9β, 10α, 17α-pregna-4,6-diene-3, 20-dione. The structure is as follows:



According to one embodiment, the present invention provides a parenteral pharmaceutical composition comprising and one or more pharmaceutically acceptable excipients, wherein said composition comprises from about 1mg to about 50mg of dydrogesterone.

According to another embodiment, the present invention provides a parenteral pharmaceutical composition comprising about 1mg of dydrogesterone and one or more pharmaceutically acceptable excipients.

According to another embodiment, the present invention provides a parenteral pharmaceutical composition comprising about 5mg of dydrogesterone and one or more pharmaceutically acceptable excipients.

According to another embodiment, the present invention provides a parenteral pharmaceutical composition comprising about 10mg of dydrogesterone and one or more pharmaceutically acceptable excipients.

According to another embodiment, the present invention provides a parenteral pharmaceutical composition comprising about 20mg of dydrogesterone and one or more pharmaceutically acceptable excipients.

According to another embodiment, the present invention provides a parenteral pharmaceutical composition comprising dydrogesterone, wherein the pharmaceutical composition is having a pH in the range of about 2 to about 11.

According to another embodiment, the present invention provides a parenteral pharmaceutical composition comprising dydrogesterone, wherein the pharmaceutical composition is having a pH in the range of about 5 to about 9.

According to another embodiment, the present invention provides a parenteral pharmaceutical composition comprising dydrogesterone, wherein the pharmaceutical composition is having a pH in the range of about 6 to about 8.

According to another embodiment, the present invention provides a parenteral pharmaceutical composition comprising about 0.1% w/v to about 10% w/v of dydrogesterone, about 0.01% w/v to about 80 % w/v of solubilizing agent(s), and one or more pharmaceutically acceptable excipients.

According to another embodiment, the present invention provides a parenteral pharmaceutical composition comprising about 0.1% w/v to about 10% w/v of dydrogesterone, about 0.01% w/v to about 80 % w/v of solubilizing agent(s), one or more carrier(s), and one or more pharmaceutically acceptable excipients.

According to another embodiment, the present invention provides a parenteral pharmaceutical composition comprising about 0.1% w/v to about 10% w/v of dydrogesterone, about 0.01% w/v to about 90 % w/v of one or more carrier(s), and one or more pharmaceutically acceptable excipients.

According to another embodiment, the present invention provides a parenteral pharmaceutical composition comprising about 1mg to about 50mg of dydrogesterone, about 0.01% w/v to about 90 % w/v of one or more carrier(s), and one or more pharmaceutically acceptable excipients.

According to another embodiment, the present invention provides a parenteral pharmaceutical composition comprising about 1mg to about 50mg of dydrogesterone, about 0.01% w/v to about 90 % w/v of one or more carrier(s), and one or more pharmaceutically acceptable excipients, wherein the pharmaceutical composition is in the form of non-aqueous composition.

According to another embodiment, the present invention provides a parenteral pharmaceutical composition comprising about 1mg to about 50mg of dydrogesterone, about 0.01% w/v to about 90 % w/v of one or more carrier(s), and one or more pharmaceutically acceptable excipients, wherein the carrier(s) is selected from the group

comprising sesame oil, castor oil, cottonseed oil, corn oil, arachis oil, mineral oil, sunflower oil, soybean oil or combinations thereof.

According to another embodiment, the present invention provides a parenteral pharmaceutical composition comprising about 1mg to about 50mg of dydrogesterone, about 0.01% w/v to about 90 % w/v of one or more carrier(s), and one or more pharmaceutically acceptable excipients, wherein the carrier(s) is selected from the group comprising one or more oil(s), solvent(s) or combination thereof, wherein the one or more oil(s) is selected from the group comprising sesame oil, castor oil, cottonseed oil, corn oil, arachis oil, mineral oil, sunflower oil, soybean oil or combinations thereof.

According to another embodiment, the present invention provides a parenteral pharmaceutical composition comprising about 1 mg to about 50 mg of dydrogesterone, one or more carrier(s) and one or more pharmaceutically acceptable excipients; wherein dydrogesterone and one or more carrier(s) are present in a molar ratio of about 1:1 to about 1:40.

According to another embodiment, the present invention provides a parenteral pharmaceutical composition comprising about 1 mg to about 50 mg of dydrogesterone, one or more carrier(s) and one or more pharmaceutically acceptable excipients; wherein dydrogesterone and one or more carrier(s) are present in a molar ratio of about 1:1 to about 1:60.

According to another embodiment, the present invention provides a parenteral pharmaceutical composition comprising about 1 mg to about 50 mg of dydrogesterone, one or more carrier(s) and one or more pharmaceutically acceptable excipients; wherein dydrogesterone and one or more carrier(s) are present in a molar ratio of about 1:1 to about 1:90.

According to another embodiment, the present invention provides a parenteral pharmaceutical composition comprising dydrogesterone and one or more pharmaceutically acceptable excipients, wherein the one or more pharmaceutically acceptable excipients are selected from the group comprising solubilizing agent(s), buffering agent(s), antioxidant(s), chelating agent(s), carrier(s), preservative(s), tonicity

agent(s), pH adjusting agent(s) and/or combinations thereof.

According to another embodiment, the present invention provides a parenteral pharmaceutical composition comprising about 1 mg to about 50 mg of dydrogesterone, about 0.01% w/v to about 80 % w/v of solubilizing agent(s), and one or more pharmaceutically acceptable excipients, wherein the one or more pharmaceutically acceptable excipients are selected form the group comprising:

(a) buffering agent(s) in an amount of about 0.01% w/v to about 20 % w/v,
(b) preservative(s) in an amount of about 0.001% w/v to about 20% w/v,
(c) tonicity agent(s) in an amount of about 0.01% w/v to about 10% w/v,
(d) chelating agent(s) in an amount of about 0.001% w/v to about 10% w/v,
(e) antioxidant(s) in an amount of about 0.001% w/v to about 10% w/v, of the pharmaceutical composition.

According to another embodiment, the present invention provides a parenteral pharmaceutical composition comprising about 1 mg to about 50 mg of dydrogesterone, and one or more pharmaceutically acceptable excipients, wherein the one or more pharmaceutically acceptable excipients are selected form the group comprising:

(a) solubilizing agent(s) in an amount of about 0.01% w/v to about 80 % w/v,
(b) buffering agent(s) in an amount of about 0.01% w/v to about 20 % w/v,
(c) preservative(s) in an amount of about 0.001% w/v to about 20% w/v,
(d) carrier(s) in an amount of about 0.01% w/v to about 90% w/v,
(e) tonicity agent(s) in an amount of about 0.01% w/v to about 10% w/v,
(f) chelating agent(s) in an amount of about 0.001% w/v to about 10% w/v,
(g) antioxidant(s) in an amount of about 0.001% w/v to about 10% w/v, of the pharmaceutical composition.

According to another embodiment, the present invention provides a parenteral pharmaceutical composition comprising about 1 mg to about 50 mg of dydrogesterone, and one or more pharmaceutically acceptable excipients, wherein the one or more pharmaceutically acceptable excipients are selected form the group comprising:

(a) solubilizing agent(s) in an amount of about 0.01% w/v to about 80 % w/v,
(b) one or more carrier(s) in an amount of about 0.01% w/v to about 95% w/v,
(c) buffering agent(s) in an amount of about 0.01% w/v to about 20 % w/v,

(d) preservative(s) in an amount of about 0.001% w/v to about 20% w/v,
(e) tonicity agent(s) in an amount of about 0.01% w/v to about 10% w/v,
(f) chelating agent(s) in an amount of about 0.001% w/v to about 10% w/v,
(g) antioxidant(s) in an amount of about 0.001% w/v to about 10% w/v, of the pharmaceutical composition.

According to another embodiment, the present invention provides a preservative free parenteral composition comprising about 1 mg to about 50 mg of dydrogesterone, about 0.01% w/v to about 80 % w/v of solubilizing agent(s), and one or more pharmaceutically acceptable excipients, wherein the one or more pharmaceutically acceptable excipients are selected form the group comprising:

(a) buffering agent(s) in an amount of about 0.01% w/v to about 20 % w/v,
(b) tonicity agent(s) in an amount of about 0.01% w/v to about 10% w/v,
(c) carrier(s) in an amount of about 0.01% w/v to about 90% w/v,
(d) chelating agent(s) in an amount of about 0.001% w/v to about 10% w/v,
(e) antioxidant(s) in an amount of about 0.001% w/v to about 10% w/v, of the pharmaceutical composition.

According to another embodiment, the present invention provides a parenteral pharmaceutical composition comprising dydrogesterone, solubilizing agent(s) and one or more pharmaceutically acceptable excipient, wherein the dydrogesterone and solubilizing agent(s) is present in a molar ratio of about 1:1 to about 1:20.

According to another embodiment, the present invention provides a stable preservative free parenteral pharmaceutical composition comprising about 1 mg to about 50 mg of dydrogesterone, about 0.01% w/v to about 80 % w/v of solubilizing agent(s), and one or more pharmaceutically acceptable excipients, wherein the one or more pharmaceutically acceptable excipients are selected form the group comprising:

(a) buffering agent(s) in an amount of about 0.01% w/v to about 20 % w/v,
(b) tonicity agent(s) in an amount of about 0.01% w/v to about 10% w/v,
(c) chelating agent(s) in an amount of about 0.001% w/v to about 10% w/v,
(d) carrier(s) in an amount of about 0.01% w/v to about 90% w/v,
(e) antioxidant(s) in an amount of about 0.001% w/v to about 10% w/v, of the composition,

wherein the pharmaceutical composition is having total impurity less than about 5%, when stored at 40°C ± 5°C & 75% ± 5% RH for a period of at least three months.

According to another embodiment, the present invention provides a stable preservative free parenteral pharmaceutical composition comprising about 1 mg to about 50 mg of dydrogesterone, about 0.01% w/v to about 90 % w/v of carrier(s), and one or more pharmaceutically acceptable excipients, wherein the one or more pharmaceutically acceptable excipients are selected form the group comprising:

(a) buffering agent(s) in an amount of about 0.01% w/v to about 20 % w/v,
(b) tonicity agent(s) in an amount of about 0.01% w/v to about 10% w/v,
(c) chelating agent(s) in an amount of about 0.001% w/v to about 10% w/v,
(d) antioxidant(s) in an amount of about 0.001% w/v to about 10% w/v, of the composition,

wherein the pharmaceutical composition is having total impurity less than about 5%, when stored at 40°C ± 5°C & 75% ± 5% RH for a period of at least three months.

According to another embodiment, the present invention provides a parenteral pharmaceutical composition comprising dydrogesterone, wherein the pharmaceutical composition is having total dydrogesterone impurity is less than 1.5%, when stored at 40°C ± 5°C & 75% ± 5% RH for a period of at least three months.

According to another embodiment, the present invention provides a stable parenteral pharmaceutical composition comprising dydrogesterone, dydrogesterone impurity A, dydrogesterone impurity B, dydrogesterone impurity C and one or more pharmaceutically acceptable excipients.

According to another embodiment, the present invention provides a stable parenteral pharmaceutical composition comprising dydrogesterone, one or more of dydrogesterone impurity selected from the group comprising dydrogesterone impurity A, dydrogesterone impurity B, dydrogesterone impurity C or combinations thereof and one or more pharmaceutically acceptable excipients, wherein the pharmaceutical composition is free of preservative.

According to another embodiment, the present invention provides a parenteral

pharmaceutical composition comprising dydrogesterone, wherein the pharmaceutical composition is having dydrogesterone impurity A is less than 0.5%, preferably less than 0.1%, more preferably less than 0.08%, when stored at 40°C ± 5°C & 75% ± 5% RH for a period of at least three months.

According to another embodiment, the present invention provides a parenteral pharmaceutical composition comprising dydrogesterone, wherein the pharmaceutical composition is having dydrogesterone impurity B is less than 0.5%, preferably less than 0.05%, when stored at 40°C ± 5°C & 75% ± 5% RH for a period of at least three months.

According to another embodiment, the present invention provides a parenteral pharmaceutical composition comprising dydrogesterone, wherein the pharmaceutical composition is having dydrogesterone impurity C is less than 0.5%, preferably less than 0.1%, more preferably less than 0.06%, when stored at 40°C ± 5°C & 75% ± 5% RH for a period of at least three months.

According to another embodiment, the present invention provides a parenteral pharmaceutical composition comprising about 1 mg to about 50 mg of dydrogesterone, Hydroxypropyl-β-cyclodextrin, one or more pharmaceutically acceptable excipients and water for injection; wherein dydrogesterone and Hydroxypropyl-β-cyclodextrin are present in a molar ratio of about 1:1 to about 1:20.

According to another embodiment, the present invention provides a parenteral pharmaceutical composition comprising about 1 mg to about 50 mg of dydrogesterone, Hydroxypropyl-β-cyclodextrin, ethanol, and one or more pharmaceutically acceptable excipients, wherein the one or more pharmaceutically acceptable excipients are selected form the group comprising:

(a) buffering agent(s) in an amount of about 0.01% w/v to about 20 % w/v,
(b) preservative(s) in an amount of about 0.001% w/v to about 20% w/v,
(c) tonicity agent(s) in an amount of about 0.01% w/v to about 10% w/v,
(d) chelating agent(s) in an amount of about 0.001% w/v to about 10% w/v,
(e) antioxidant(s) in an amount of about 0.001% w/v to about 10% w/v, of the pharmaceutical composition.

According to another embodiment, the present invention provides a parenteral pharmaceutical composition comprising about 1 mg to about 20 mg of dydrogesterone, about 1% w/v to about 50 % w/v of Hydroxypropyl-β-cyclodextrin, about 1% v/v to about 50% v/v of ethanol, one or more pharmaceutically acceptable excipients, and water for injection.

According to another embodiment, the present invention provides a parenteral pharmaceutical composition comprising dydrogesterone, wherein the pharmaceutical composition is having an Osmolality in the range of about 200mOsmol/kg to about 9000mOsmol/kg, preferably about 2000mOsmol/kg to about 7000mOsmol/kg, more preferably about 4500mOsmol/kg to about 5500mOsmol/kg.

According to another embodiment, the present invention provides a parenteral pharmaceutical composition comprising dydrogesterone, wherein the pharmaceutical composition is having a viscosity in the range of about 4cps to about 8cps, preferably about 5cps to about 6cps, when measured at 205 shear rate.

According to another embodiment, the present invention provides a parenteral pharmaceutical composition comprising dydrogesterone, wherein the pharmaceutical composition comprising less than 6000 particulate matter having size less than 10µm.

According to another embodiment, the present invention provides a parenteral pharmaceutical composition comprising dydrogesterone, wherein the pharmaceutical composition comprising less than 600 particulate matter having size less than 25µm.

According to another embodiment, the present invention provides a parenteral pharmaceutical composition comprising dydrogesterone, wherein dydrogesterone are present/used in with the particle size in the range of D90 less than 200 microns (µ), preferably in the range of D90 less than 100 microns.

According to another embodiment, the present invention provides a parenteral pharmaceutical composition comprising dydrogesterone, wherein the particle size of the Dydrogesterone is D90 less than 50µ.

According to another embodiment, the present invention provides a parenteral pharmaceutical composition comprising dydrogesterone, and one or more pharmaceutically acceptable excipients; wherein the composition is used for the treatment of progesterone deficiency, threatened abortion, pre-eclampsia, pre-menstrual syndrome (PMS), post-menopausal complaints, female infertility, pain during menstruation, endometriosis, irregular duration and occurrence of menstrual cycles, dysfunctional uterine bleeding and/or heavy menstrual bleeding.

According to another embodiment, the present invention provides a process of preparation of a parenteral pharmaceutical composition comprising dydrogesterone, wherein said process comprises:

(a) mixing dydrogesterone and one or more pharmaceutically acceptable excipients to obtain a clear solution;

(b) adding optionally, other pharmaceutically acceptable excipients to solution of step (a);

(c) making up the volume of solution of step (b) to 100%; and

(d) filtering the solution and then filling in suitable container(s).

According to another embodiment, the present invention provides a process of preparation of a parenteral pharmaceutical composition comprising dydrogesterone, wherein said process comprises:

(a) mixing dydrogesterone and one or more pharmaceutically acceptable carrier(s) to obtain a clear solution;

(b) adding optionally, other pharmaceutically acceptable excipients to solution of step (a);

(c) making up the volume of solution of step (b) to 100%; and

(d) filtering the solution and then filling in suitable container(s).

According to another embodiment, the present invention provides a process of preparation of a parenteral pharmaceutical composition comprising dydrogesterone, wherein said process comprises:

(a) collecting water in a suitable vessel;

(b) adding carrier(s), one or more pharmaceutically acceptable excipients, and dydrogesterone, simultaneously or one after the other to step (a) to obtain a clear

solution;

(c) adding optionally, one or more other pharmaceutically acceptable excipients to the solution of step (b);

(d) adjusting optionally, pH of the solution of step (b) or (d);

(e) making up the volume of the solution of step (b) or adjusting pH of solution of step (d) to 100% batch size with water; and

(f) filtering the solution of step (e) and then filling the solution in suitable container(s).

In one embodiment, the composition of the present invention can be prepared aseptically and terminally sterilized.

According to another embodiment, the present invention provides a process of preparation of a parenteral pharmaceutical composition comprising dydrogesterone, wherein said process comprises:

(a) collecting water in a suitable vessel;

(b) adding ethanol and Hydroxypropyl-β–cyclodextrin to step (a);

(c) adding dydrogesterone to step (b) with stirring of solution to obtain a clear solution;

(d) adding optionally, one or more other pharmaceutically acceptable excipients to the solution of step (c);

(e) adjusting optionally, pH of the solution of step (c) or (d);

(f) making up the volume of the solution of step (c) or adjusting pH of the solution of step (e) to 100% batch size with water; and

(g) filtering the solution of step (f) and then filling the solution in suitable container(s).

According to another embodiment, the present invention provides process of preparation of a parenteral pharmaceutical composition comprising dydrogesterone and oils, wherein said process comprises:

(a) collecting suitable quantity of one or more excipients such as ethanol, benzyl alcohol and polysorbate 80;

(b) adding dispensed quantity of dydrogesterone to the excipients of step (1) and allow to solubilize under stirring to form solution;

(c) collecting 70% of batch size of sesame oil in separate container and the solution of step 2 is added under stirring;

(d) making up the volume of solution obtained in step (c) to 100% batch size with constant stirring;

(e) filtering the solution through 0.2-micron PES/PTFE filter followed by finalizing the solution in container closure system (Glass vial/ampule).

The present invention further relates to a process for preparation of a parenteral pharmaceutical composition of dydrogesterone, wherein the process comprises inert gas purging such as Nitrogen purging to reduce the oxygen concentration or flushing with oxygen-free gas, substitution with oxygen-free gas, or bubbling with oxygen-free gas such as Nitrogen.

The present invention further relates to a package or storage container for packaging or storing the parenteral pharmaceutical composition, wherein the package or container is made up of material that blocks oxygen or is impervious to oxygen or comprises an oxygen scavenger.

The pharmaceutical compositions as per the present invention can be bulk sterilized and/or terminally sterilized using any methods, such as filtration, moist heat, dry heat, gas sterilization or irradiation (gamma and electron beam). The container in which composition is filled can be sterilized using oven, autoclaving, gamma irradiation or ethylene oxide or pre-acetic acid or any other conventional method of sterilization.

Another embodiment of the present invention is to provide a parenteral pharmaceutical composition comprising dydrogesterone and one or more pharmaceutically acceptable exceptions, wherein the composition is in the form of injection or injection vials.

Another embodiment of the present invention is to provide a parenteral pharmaceutical composition comprising dydrogesterone, wherein the pharmaceutical composition may be given in single dose or as divided dose administered at appropriate intervals i.e. two, three, four or more sub-doses per patient per day, with or without food.

Another embodiment of the present invention is to provide a parenteral pharmaceutical composition comprising dydrogesterone, wherein the pharmaceutical composition may

be given once daily, twice daily, thrice daily, 4 times a day, 5 times a day, or at appropriate interval, with or without food.

In another embodiment of the present invention, there is provided a stable parenteral pharmaceutical composition of dydrogesterone, wherein the composition is having impurities below FDA acceptable daily intake limit. The total impurity(ies) of about 5% or less, 4% or less, 3% or less, 2% or less, or 1% or less at 40 °C ± 5 °C and 75% ± 5% RH for a period of at least three months.

The terms "FDA acceptable intake limit" of impurity(ies) as used in the present invention is the upper limit set by FDA for daily intake of impurity(ies) below which there is no harmful side-effect likely to occur on long term treatment with the therapeutically active agent.

Suitable "pharmaceutically acceptable excipients" include, without limitation, solubilizing agent(s), buffering agent(s), antioxidant(s), chelating agent(s), carrier(s), preservative(s), tonicity agent(s), pH adjusting agent(s) and/or combinations thereof.

Suitable solubilizing agents include, without limitation, surfactants, lipids, organic liquids/semi-solids, cyclic oligosaccharides/cyclodextrins, phospholipids, or mixtures thereof. The solubilizing agent(s) may be employed in an amount ranging from about 0.01% w/v to about 80% w/v of the pharmaceutical composition.

Suitable surfactants include, without limitation, poloxamers, polysorbates, alkylaryl polyethers, polyoxyethyleneglycol alkyl ethers, tyloxapol, and polyoxyls. Poloxamers are nonionic triblock copolymers composed of a central hydrophobic chain of polyoxypropylene (poly (propylene oxide)) flanked by two hydrophilic chains of polyoxyethylene (poly (ethylene oxide)). Polysorbates are oily liquids derived from ethoxylated sorbitan esterified with fatty acids. Cyclodextrins are composed of 5 or more α-D-glucopyranoside units linked together at position 1 and 4. Polyoxyls are a mixture of mono- and diesters of stearate and polyoxyethylene diols. Preferred embodiments include but are not limited to poloxamer 188 (such as Pluronic® F-68) and poloxamer 407 (such as Pluronic® F127); polysorbate 20, polysorbate 60, polysorbate 80, tyloxapol, Brij® 35, Brij® 78, Brij® 98 and Brij® 700, Span® 20, Span® 40, Span® 60, Span® 80;

and polyoxylspolyoxyl 40 stearate, polyoxyl 30 castor oil, polyoxyl 35 castor oil, and polyoxyl 40 hydrogenated castor oil; Hydrogenated Castor oil (or PEG (40 Hydrogenated castor oil) (HCO-40) or combinations thereof. In preferred embodiment, the surfactant includes, without limitaion non-ionic surfactants such as Kolliphore EL (Cremophor EL), Cremophor RH 40, Cremophor RH 60, *d*-α-tocopherol polyethylene glycol 1000 succinate, polysorbate 20, polysorbate 80, Solutol HS 15, sorbitan monooleate, poloxamer 407, Labrafil M-1944CS, Labrafil M-2125CS, Labrasol, Gellucire 44/14, Softigen 767, and mono- and di-fatty acid esters of PEG 300, 400, or 1750, and combinations thereof. When present, a non-ionic surfactant may be employed in an amount ranging from about 0.01% w/v to about 50% w/v of the pharmaceutical composition.

Suitable carrier(s) includes, but not limited to, purified water, water for injection, bacteriostatic water for injection, sterile water, isotonic saline water, buffered aqueous solution, ethanol, methanol, isopropyl alcohol, glycerin, propylene glycol, sesame oil, castor oil, arachis oil, mineral oil, sunflower oil, soybean oil, peppermint oil, corn oil, peanut oil, olive oil, cotton seed oil, hydrogenated vegetable oils, hydrogenated soybean oil, and medium-chain triglycerides of coconut oil, palm seed oil, polyethylene glycol (PEG) propylene glycol (PG), sorbitol, glycerine, acetone, benzyl alcohol, dimethyl sulfoxide, N-methyl-2-pyrrolidone, glycofurol, solketal, glycerol formal or combinations thereof. When present, carrier(s) may be employed in an amount ranging from about 0.01% w/v to about 90% w/v of the pharmaceutical composition.

Suitable organic liquids/semi-solids include, without limitation, beeswax, *d*-α-tocopherol, oleic acid, vegetable oils, ethyl oleate, propylene glycol, and polyethylene glycol, isopropyl myristate, glycerine, medium-chain mono- and di- glycerides, and combinations thereof. When present, organic liquids/semi-solids may be employed in an amount ranging from about 0.01% w/v to about 50% w/v of the pharmaceutical composition.

Suitable cyclic oligosaccharides/cyclodextrins include, without limitation, α-cyclodextrin, β-cyclodextrin, hydroxypropyl-β-cyclodextrin, and sulfobutylether-β-cyclodextrin, cyclodextrins-2-HP25, ionically charged (*e.g.* anionic) β-cyclodextrins with or without a butyrated salt (Captisol®), hydroxypropyl-gamma-cyclodextrin,

gamma cyclodextrin, and combinations thereof. When present, a cyclodextrin may be employed in an amount ranging from about 0.01% w/v to about 50% w/v of the pharmaceutical composition.

Suitable phospholipids include, without limitation, hydrogenated soy phosphatidyl choline, distearoyl phosphatidyl glycerol, l-α-dimyristoylphosphatidylcholine, l-α-dimyristoyl phosphatidyl glycerol, and combinations thereof. When present, phospholipid(s) may be employed in an amount ranging from about 0.01% w/v to about 50% w/v of the pharmaceutical composition.

Suitable buffering agent(s) include, without limitation, to phosphate buffer, acetate buffer, citrate buffer, succinate buffer, borate buffers, tris HCl and amino acids such as glycine, aspartate, histidine, cysteine, tyrosine, phenylalanine, proline, arginine, threonine, serine, valine, isoleucine, lycine, and glutamine. The particular concentration of the buffer will differ, depending on the specific agent employed. When present, the buffering agent(s) is preferably used in an amount of about 0.01% w/v to about 20% w/v of the pharmaceutical composition.

Suitable tonicity agent(s) include, without limitation, sodium chloride, potassium chloride, magnesium chloride, calcium chloride, non-ionic diols such as glycerol and propylene glycol, dextrose and/or mannitol, sorbitol. Amount of tonicity agent will vary, depending on the certain agent to be added. When present, the tonicity agent(s) is preferably used in an amount of about 0.01% w/v to about 10% w/v of the pharmaceutical composition.

Suitable preservative includes, without limitation, benzalkonium chloride (BAC), chlorhexidine gluconate, benzethonium chloride, cetyl pyridinium chloride, benzyl bromide, benzyl alcohol, ethanol, phenylmercury nitrate, phenylmercury acetate, thiomerosal, merthiolate, phenylmercuryborate, methylparaben, propylparaben, sorbic acid, potassium sorbate, sodium benzoate, sodium propionate, ethyl p-hydroxybenzoate, butyl-p-hydroxybenzoate, chlorobutanol, sorbic acid, polyquaternary ammonium compounds, ascorbic acid, butylated hydroxyl toluene (BHT), butylated hydroxyl anisole (BHA), benzoic acid, citric acid, edetic acid, parabens, phenol, propyl gallate, sodium bisulfite, sodium sulfite, chlorocresol, cresol, dehydroacetic acid, phenol,

potassium benzoate, potassium sorbate, sodium dehydroacetate, sodium propionate, thymol, butylparaben, ethylparaben, methylparaben, methylparaben sodium, propylparaben, propylparaben sodium, thimerosal and the various salt forms for these compounds, or combinations thereof. When present, the preservative(s) may be used in an amount of about 0.001% w/v to about 20.0% w/v of the pharmaceutical composition.

According to one embodiment of the present invention the pharmaceutical composition is free of preservative.

Suitable chelating agent(s) includes, without limitation, ethylenediaminetetraacetic acid and metal salts thereof, such as disodium edetate, trisodium edetate, tetrasodium edetate or mixtures thereof. When present, the chelating agent(s) may be added in an amount of about 0.001% w/v to about 10.0% w/v of the pharmaceutical composition.

Suitable antioxidant(s) include, but are not limited to, sodium thiosulfate, sodium bisulfite, acetone sodium bisulfite, gentisic acid, gentisic acid ethanolamide, sodium formaldehyde sulfoxylate, thiourea, butylated hydroxyanisole, butylated hydroxy toluene, esters of gallic acid, ascorbic acid, salts of ascorbic acids such as ascorbyl palmitate, tartaric acid, citric acid, fumaric acid, malic acid, sodium ascorbate, retinoids and derivatives of vitamin A, acetylcysteine, thioglycerol, sodium metabisufite, sodium sulphite, sodium pyrosulphate, methionine, glutamine, thiamine, Vitamin E and its derivatives e.g. Vitamin E TPGS and/or combinations thereof.

The pH adjusting agent is typically a mineral acid or metal hydroxide base preferably selected from the group of potassium hydroxide, sodium hydroxide, hydrochloric acid, or mixtures thereof, and preferably sodium hydroxide and/or hydrochloric acid. These acidic and/or basic pH adjusting agents are added to adjust the formulation to the target pharmaceutically acceptable pH range. Hence, it may not be necessary to use both acid and base - depending on the formulation, the addition of one of the acid or base may be sufficient to bring the mixture to the desired pH range.

The compositions will typically have a pH in the range of 2 to 11, preferably 2 to 8, more preferably 4 to 8.

The composition will typically have a pH in the range of 2 to 11, preferably 6 to 8, more preferably 7 to 9.

While selected embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this invention belongs. All patents and publications referred to herein are incorporated by reference.

EXAMPLES

The present invention is further illustrated by the following examples which are provided merely to be exemplary of the invention and don't limit the scope of the invention. Certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

Table 1: Parenteral pharmaceutical composition of Dydrogesterone

Ingredient	**%w/v of the total composition**
Dydrogesterone	0.1-10%
Solubilizing agent(s)	0.01-80%
Carrier(s)	0.01-90%
Buffering agent(s)	0.01-20%
Preservative(s)	0.001-20%
Tonicity agent(s)	0.01-10%
Antioxidant(s)	0.001-10%
Chelating agent(s)	0.001-10%
pH adjusting agent(s)	q.s.

Table 2: Parenteral Pharmaceutical composition of Dydrogesterone

Name of Ingredient	Example 2	Example 3	Example 4	Example 5
Dydrogesterone	10mg	10mg	10mg	10mg
Hydroxypropyl-β-cyclodextrin	-	-	225mg	225mg
PEG 400	0.20ml	-	-	-
Ethanol	0.50ml	0.60ml	0.50ml	0.30ml
N-methyl pyrrolidone	0.19ml	0.19ml	-	-
Sodium chloride	9mg	9mg	9mg	-
Water for injection	q.s. to 1ml	q.s. to 1ml	q.s. to 1ml	q.s. to 1ml

Buffer and pH Adjusting agent to adjust pH ~7, if required.

The pharmaceutical composition of Example 5 was prepared and subjected to the stability study to access the stability of composition after storage. The composition has prepared and charged into the stability chamber with varying temperature and humidity conditions. The results are given in below table 3.

Table 3: Stability study of the Parenteral composition of Dydrogesterone

	Initial	**40°C/75% RH**		**30°C/65 % RH**	**30°C/75 % RH**	**25°C/60 % RH**
		1M	**3M**	**3M**	**3M**	**3M**
Osmolality (mOsmol/kg)	5070	4840	5180	5240	5190	5010
Ethanol Content by GC (mg/ml)	230.81	225.38	203.19	205.18	202.23	211.18
Assay by HPLC	10.29 (102.85%)	10.35 (103.46%)	10.22 (102.21%)	10.23 (102.31%)	10.22 (102.19%)	10.32 (103.24%)
Organic Impurities (wt%, By HPLC)						
Dydrogesterone Impurity-A at 385nm	**0.05**	**0.05**	**0.02**	**0.02**	**0.01**	**0.02**
Dydrogesterone Impurity-B	0.03	0.03	0.03	0.03	0.03	0.03

Dydrogesterone Impurity-C	0.06	0.06	0.07	0.07	0.07	0.06
Any unspecified impurity	ND	ND	ND	ND	ND	ND
Total Impurities	**0.14**	**0.14**	**0.12**	**0.12**	**0.11**	**0.11**

Stability was measured in terms of the total impurity. From the above table 3, it is evident that the composition of dydrogesterone is stable. The total impurity is same or decreases partially after storing 3 months in stability chamber with varying conditions.

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Table 4: Parenteral Pharmaceutical composition of Dydrogesterone

Name of Ingredient	**Example 6**	**Example 7**	**Example 8**	**Example 9**
Dydrogesterone	5mg	5mg	5mg	5mg
Hydroxypropyl-β-cyclodextrin	-	-	225mg	225mg
PEG 400	0.20ml	-	-	-
Ethanol	0.50ml	0.60ml	0.50ml	0.30ml
N-methyl pyrrolidone	0.19ml	0.19ml	-	-
Sodium chloride	9mg	9mg	9mg	-
Water for injection	q.s. to 1ml	q.s. to 1ml	q.s. to 1ml	q.s. to 1ml

Buffer and pH Adjusting agent to adjust pH ~7, if required.

Table 5: Pharmaceutical composition of Dydrogesterone

Name of Ingredient	**Example 10**	**Example 11**	**Example 12**	**Example 13**	**Example 14**	**Example 15**
Dydrogesterone	10mg	10mg	10mg	10mg	10mg	10mg
Hydroxypropyl-β-cyclodextrin	450mg	450mg	360mg	270mg	135mg	225mg
Ethanol	-	-	0.3ml	0.3ml	0.4ml	0.2ml
N-methyl pyrrolidone	-	-	-	-	0.15ml	0.15ml
Sodium	-	9mg	-	-	-	-

chloride						
Water for injection	q.s. to 1ml	q.s. to 1ml	q.s. to 1ml	q.s. to 1ml	q.s. to 1ml	q.s. to 1ml

Buffer and pH Adjusting agent to adjust pH ~7, if required.

Table 6: Pharmaceutical composition of Dydrogesterone

Ingredients	**Example 16**	**Example 17**	**Example 18**	**Example 19**	**Example 20**
Dydrogesterone (Micronized)	5.0 mg	10.0 mg	10.0 g	25.0 g	25.0 g
Hydroxypropyl β-cyclodextrin	225.0 mg	225.0 mg	450.0 g	562.5 g	1125.0 g
Ethanol	237.0 mg	237.0 mg	474.0 g	592.5 g	1185.0 g
Water for Injection	q.s. to 1 mL	q.s. to 1 mL	q.s. to 2000 mL	q.s. to 2500 mL	q.s. to 5000 mL

Process:

1. Collected 70% of batch size of water for injection (WFI) and nitrogen purged for 30 – 60 min.
2. Collected 30% of batch size of nitrogen purged WFI from step 1 in suitable container.
3. Accurately weigh absolute ethanol and added to step 2 WFI and stirring.
4. Accurately weigh Hydroxypropyl β-cyclodextrin in glass beaker and added to Step 3 solution under stirring to get clear solution.
5. Dydrogesterone is added to the solution obtained in step 4 under stirring until the dydrogesterone completely solubilized.
6. Make up the volume to 100% batch size using nitrogen purged WFI and stir the solution to obtained uniform solution.
7. Solution obtained in step 6 was filtered using 0.2 µm polyethersulfone membrane filter and stir the filtered solution to obtain uniform solution
8. Filtered solution is filled as 1 mL in 2 mL clear glass vial using peristaltic pump.
9. Alternatively, the contents of vials/ampoules can be terminally sterilized.

Table 7: Pharmaceutical composition of Dydrogesterone

Name of Ingredient	Example 21	Example 22
Dydrogesterone	20 mg	20 mg
Ethanol	0.25ml	0.25ml
Benzyl Alcohol	0.12ml	0.12ml
Propylene glycol	0.25ml	0.18ml
Water for injection (WFI)	q.s. to 1ml	q.s. to 1ml

Process:

1. Collected water for injection in a vessel.
2. Added ethanol, propylene glycol, benzyl alcohol to water for injection of step 1 with stirring.
3. Added dydrogesterone and kept stirring till clear solution is formed.
4. Optionally, adjusted the pH.
5. Made up the volume with water for injection to 100% batch size.
6. Filtered the solution and then filled in glass vial(s).
7. Optionally, autoclaved at 121° C for 15 - 30 min at 15 psi.

Table 8: Pharmaceutical composition of Dydrogesterone

Ingredient	Example 23	Example 24	Example 25	Example 26	Example 27	Example 28
Dydrogesterone	5 mg	5 mg	5 mg	5 mg	10 mg	15 mg
Ethanol	300 µL	-	-	-	-	-
Benzyl alcohol	-	12 mg	30 mg	-	50 mg	50 mg
Polysorbate 80	5 mg	-	-	-	-	-
Sesame oil	q.s. to 1 mL	q.s. to 1 mL	q.s. to 1 mL	q.s. to 1 mL	q.s. to 1 mL	q.s. to 1 mL

Process:

1. Collected suitable quantity of one or more excipients such as ethanol, benzyl alcohol and/or polysorbate 80.

2. Added dispensed quantity of dydrogesterone to the excipients of step (1) and allow to

solubilize under stirring to form solution.

3. 70% of batch size of sesame oil is collected in separate container and the solution of step 2 to be added under stirring.

4. Make up the volume of solution obtained in step (3) to 100% batch size with constant stirring.

5. Solution is filtered through 0.2-micron PES/PTFE filter.

6. Solution is filled in finalized container closure system (Glass vial/ampule)

Table 9: Pharmaceutical composition of Dydrogesterone

Ingredient	**Example 29**	**Example 30**	**Example 31**	**Example 32**	**Example 33**
Dydrogesterone	5 mg	5 mg	5 mg	5 mg	10 mg
Ethanol	100 mg	-	-	-	
Benzyl alcohol	100 mg	-	30 mg	20 mg	50
Benzyl benzoate	150 mg	500 mg	400 mg	460 mg	450 mg
Castor oil	q.s. to 1 mL	q.s. to 1 mL	q.s. to 1 mL	q.s. to 1 mL	q.s. to 1 mL

Table 10: Pharmaceutical composition of Dydrogesterone

Ingredient	**Example 34**	**Example 35**	**Example 36**	**Example 37**
Dydrogesterone	10 mg	5 mg	5 mg	5 mg
Ethanol		-	-	-
Benzyl alcohol	50	12 mg	20mg	12mg
Benzyl benzoate	450 mg	-	500 mg	500 mg
Castor oil	q.s. to 1 mL	q.s. to 1 mL	q.s. to 1 mL	q.s. to 1 mL

Process:

1. Collected suitable quantity of one or more excipients such as ethanol and/or benzyl alcohol.

2. Added dispensed quantity of dydrogesterone to the excipients of step (1) and allow to solubilize under stirring to form solution.

3. 30% of batch size of castor oil is collected in separate container and the solution of step 2 to be added under stirring.

4. Make up the volume of solution obtained in step (3) to 100% batch size with constant stirring.

5. Solution is filtered through 0.2-micron PES/PTFE filter.

6. Solution is filled in finalized container closure system (Glass vial/ampule)

Dated this the 08th day of December 2023. **For Mankind Pharma Ltd.**

Dr. Anil Kumar
Chief Scientific Officer

We Claim:

1. A parenteral pharmaceutical composition comprising dydrogesterone and one or more pharmaceutically acceptable excipient.

2. The parenteral pharmaceutical composition as claimed in claim 1, wherein the dydrogesterone is present in amount of about 1mg to about 50mg.

3. The parenteral pharmaceutical composition as claimed in claim 1, wherein the pharmaceutical composition is an aqueous or a non-aqueous composition.

4. The parenteral pharmaceutical composition as claimed in claim 1, wherein the pharmaceutical composition is an aqueous composition and comprises water as carrier.

5. The parenteral pharmaceutical composition as claimed in claim 1, wherein the pharmaceutical composition is non-aqueous composition and comprises oil or alcohol or mixtures thereof as carrier.

6. The parenteral pharmaceutical composition as claimed in claim 4 and 5, wherein the pharmaceutical composition further comprises solubilizing agent(s).

7. The parenteral pharmaceutical composition as claimed in claim 6, wherein the solubilizing agent(s) is present in amount of about 0.01% w/v to about 80 % w/v.

8. The parenteral pharmaceutical composition as claimed in claim 6, wherein the solubilizing agent(s) is selected from the group comprises of surfactants, lipids, organic liquids, organic semi-solids, cyclic oligosaccharides, cyclodextrins, phospholipids, or mixtures thereof.

9. The parenteral pharmaceutical composition as claimed in claim 6, where in the solubilizing agents are selected from the group comprising polysorbate or cyclodextrins or derivative or salts thereof.

10. The parenteral pharmaceutical composition as claimed in claim 1, wherein the one or more pharmaceutically acceptable excipient is selected from the group comprising solubilizing agent(s), buffering agent(s), antioxidant(s), chelating agent(s), carrier(s), preservative(s), tonicity agent(s), pH adjusting agent(s) and/or combinations thereof.

11. The parenteral pharmaceutical composition as claimed in claim 1, wherein the said composition is having total impurity less than about 5% at 40°C ± 5°C and 75% ± 5% RH for a period of at least three months.

12. The parenteral pharmaceutical composition as claimed in claim 1, wherein the parenteral composition has pH in the range of 5 to 9.

13. A parenteral pharmaceutical composition comprising dydrogesterone, solubilizing agent(s) and one or more pharmaceutically acceptable excipient, wherein the dydrogesterone and solubilizing agent(s) is present in a molar ratio of about 1:1 to about 1:20.

14. A parenteral pharmaceutical composition comprising about 1 mg to about 50 mg of dydrogesterone, and one or more pharmaceutically acceptable excipients, wherein the one or more pharmaceutically acceptable excipients are selected form the group comprising:

(a) solubilizing agent(s) in an amount of about 0.01% w/v to about 80 % w/v,
(b) one or more carrier(s) in an amount of about 0.01% w/v to about 95% w/v,
(c) buffering agent(s) in an amount of about 0.01% w/v to about 20 % w/v,
(d) preservative(s) in an amount of about 0.001% w/v to about 20% w/v,
(e) carrier(s) in an amount of about 0.01% w/v to about 90% w/v,
(f) tonicity agent(s) in an amount of about 0.01% w/v to about 10% w/v,
(g) chelating agent(s) in an amount of about 0.001% w/v to about 10% w/v,
(h) antioxidant(s) in an amount of about 0.001% w/v to about 10% w/v, of the pharmaceutical composition.

Dated this the 08th day of December 2023. **For Mankind Pharma Ltd.**

Dr. Anil Kumar
Chief Scientific Officer

A **PARENTERAL PHARMACEUTICAL COMPOSITION OF DYDROGESTERONE**

ABSTRACT

The present invention relates to a parenteral pharmaceutical composition comprising therapeutically effective amount of dydrogesterone, and one or more pharmaceutically acceptable excipients. Further, the present invention also relates to the process of preparation of the parenteral pharmaceutical composition thereof.

Dated this the 08th day of December 2023. **For Mankind Pharma Ltd.**

Dr. Anil Kumar
Chief Scientific Officer