INJECTABLE COMPOSITION

FIELD AND OBJECT OF THE INVENTION

The present patent application is directed toward compositions useful in cancer therapies.

In particular, the present invention refers to the use of a letrozole composition suitable for forming an *in situ* intramuscular implant comprising a sterile biodegradable thermoplastic polymer of polylactic acid (PLA), for administering a patient in need thereof from 0.1-2 milligrams every day.

BACKGROUND

Without doubt, cancer treatments need to be developed, not only new molecular entities but also pharmacological products for improving patients' quality of life. In this sense, the development of prolonged release formulation signifies an advance because they enable reducing the total dose administered, increasing the duration of each dose and the number of administrations and thereby create a positive impact on the emotional state of the patient.

In this sense, in the present invention, the active ingredients letrozole and anastrozole have been selected as candidate pharmaceutical drugs for this type of prolonged release formulation because they are the first line active ingredients in the adjuvant treatment of postmenopausal women with hormone receptor-positive advanced breast cancer for whom there is no alternative therapy beyond daily administration of a tablet.

Letrozole (4,4' -(1h ,2,4-triazol-1-yl)methyl)dibenzonitrile) and anastrozole (2,2' -[5- (1 H-1 ,2,4-triazol-1-yl methyl)-1 ,3-phenylene]bis(2-methylpropanen itrile)) belong to a class of drugs called non-steroidal inhibitors of aromatase and their mechanism of action consists of reducing the amount of oestrogen in the body. This effect can decelerate or stop the growth of many types of cancer-producing cells in the breast that need oestrogen to grow.

Currently there is no formulation of letrozole on the market with the ability to control the release of the drug over a long period of time. The pharmaceutical drug letrozole is currently only available in tablet form for daily oral administration (Femara®).

In the treatment of breast cancer, as in the treatment of cancer in general, the psychological state of the patient is very important; therefore the development of a three-monthly formulation of letrozole and/or anastrozole means a substantial improvement in their quality of life, reducing the impact that would result from daily treatment. In turn, medical examinations that are carried out during monitoring of the disease are normally conducted at 3 and 6 months over the first few years, so the administration of the formulation could coincide with consultancy visits to the doctor.

Similar reasoning has led to the appearance on the market of formulations such as Zoladex®, a preformed implant of goserelin for subcutaneous three-monthly application for the treatment of prostate carcinoma, and Implanon®, a preformed implant of etonogestrel used as a contraceptive. However, these preformed implants show a series of disadvantages including:

- The preparation of the implants by extrusion requires the use of high temperatures, which can cause the degradation of the active ingredient and the generation of potentially toxic impurities;
- Low homogeneity of the product obtained when including active ingredients at low doses;
- Need for surgical procedures for implanting or injection of the implant using large diameter needles.

It is also possible to find in the literature some publications on implantable compositions of letrozole and/or anastrozole such as the following:

For example, WO 2008/041245 describes implantable compositions comprising a wide variety of active ingredients such as some aromatase inhibitors, including anastrozole, in a wide variety of administration forms from preformed microparticles suspended in an aqueous vehicle to formulations that gellify *in situ*. Although it is doubtful that this document can sufficiently support all the combinations of active ingredients and administration forms that may arise, the examples always refer to preformed microparticles, that is it never describes systems of forming implants directly "*in situ*". Finally, it should be pointed out that none of the examples show a duration of over 60 days.

WO2010/065358 A1 describes compositions for the administration of medicines containing testosterone and an aromatase inhibitor for continuous administration of testosterone and for preventing its conversion to estradiol. Although the description

considers the possibility that the form of administration may be an implant, the only example of a form of administration is pellets.

Also, WO 2012/07 4883 A 1 describes biodegradable compositions for administration of pharmaceutical drugs. These compositions require the use of water-insoluble solvents such as benzyl benzoate or benzyl alcohol in order to maintain the implant in a liquid or semi-solid state. These solvents have been previously shown to provide sudden releases and therefore are not suitable for the prolonged release compositions of the present invention.

Finally, US 2008/0206303 A1 describes prolonged release formulations of anastrozole comprising a PLA or PLGA polymer that can be accompanied by a wide variety of solvents; however, in the embodiments of the invention, the solvents used are benzyl alcohol and n-methyl-2-pyrrolidone (NMP), solvents that give rise to a very large burst followed by a subsequent almost zero release. In fact, the burst that was acceptable for the inventors in this document was 25-30% in one day, a very high value, and because of this none of their examples lasted more than 60 days; in particular in dogs, animals similar to humans, release did not continue longer than 35 days. Finally, no mention was made in this document of letrozole particle size nor of the importance of this factor in the behaviour of the formulation.

Therefore, it would be desirable to obtain a three-monthly formulation of letrozole and/or anastrozole for first line adjuvant treatment of breast cancer in hormone receptor-positive postmenopausal women. For this reason, the technology of implants of the invention that are formed *in situ* overcomes the majority of the drawbacks presented by current formulations based on preformed implants. It offers an alternative practical and effective therapy for the patient achieving therapeutic profiles lasting for at least 60 days.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a letrozole composition suitable for forming an *in situ* intramuscular implant which can maintain the required letrozole plasma levels for hormone suppression during at least 6 months.

This long-term hormone suppression therapy has been shown to provide a superior clinical outcome in human compared to oral daily dosage treatment. The letrozole formulations described herein enable obtaining therapeutic levels of the drug in plasma

from the start and continuously over a period of at least six months, avoiding the need for daily dosing regimes and thereby improving the patient's quality of life.

Also, sustained lower effective letrozole plasma levels with lower doses (compared to oral treatment) reduce the adverse side effects (bone mass loss, bone/joint/muscle pain, dyslipidemia) due to lower exposure to drug. Moreover, the present invention provides a better safety profile which positively impact treatment duration adherence. The present inventors have found that the necessary dose for clinical efficacy of letrozole is much smaller than was thought. Thus, the compositions of the present invention provide an effective letrozole therapy for aromatase inhibition at least as early as the oral therapy since administration, with much smaller doses than previous compositions, providing a sustained and stable release of such low doses over long time periods (at least 6 months) and reducing the adverse side effects.

The inventors of the present invention have found that the preferred clinically suitable and superior compositions are achieved when a particular particle size for the polymer is used. Said particle size was at first believed to be irrelevant since the polymer is dissolved in the solvent when the composition is prepared before administration. However, the inventors have found that the particle size of the polymer in fact has an impact on the release of the active ingredient from the implant, and also has an impact on the clinical suitability for the implant administration, since these type of compositions need to be administered by intramuscular injection soon after reconstitution. As shown in the figures, the present compositions with controlled particle size of the poly(lactic acid) (PLA) provide a drug release from the implant that allows having lower drug plasma levels which are still effective in hormone suppression and therefore can be used for longer periods and also reduce the adverse side effects.

The present invention relates to an injectable depot composition comprising PLA having a particle size distribution as follows: particle size mass distribution with not more than 10% above 300 microns, preferably not above 250 microns, when measured by analytical sieving according to USP<786> and/or said PLA has a particle size volume distribution with a D90 not above 330 microns, preferably not above 280 microns when measured by laser diffraction analysis; and/or wherein said PLA has a particle size mass distribution where not more than 80 % of the particles have a particle size below 125 microns, when measured by analytical sieving according to USP<786> and/or said PLA has a particle size volume distribution with a D80 not below 135 microns when measured by laser diffraction analysis.

The present invention relates to a letrozole composition comprising a sterile biodegradable thermoplastic polymer of polylactic acid (PLA), wherein said PLA is milled and has a particle size mass distribution with not more than 10% above 300 microns, preferably not above 250 microns, when measured by analytical sieving according to USP<786>.

Also, the present invention relates to a letrozole composition comprising a sterile biodegradable thermoplastic polymer of polylactic acid (PLA), wherein said PLA is milled and has a particle size volume distribution with a D90 not above 330 microns, preferably not above 280 microns when measured by laser diffraction analysis.

Also, the present invention relate to a letrozole composition comprising a sterile biodegradable thermoplastic polymer of polylactic acid (PLA), wherein said PLA is milled and has a particle size mass distribution with not more than 10% above 300 microns, preferably not above 250 microns, and where not more than 80 % of the particles have a particle size below 125 microns, when measured by analytical sieving according to USP<786>.

Also, the present invention relate to a letrozole composition comprising a sterile biodegradable thermoplastic polymer of polylactic acid (PLA), wherein said PLA is milled and has a particle size mass distribution where not more than 80 % of the particles have a particle size below 125 microns, when measured by analytical sieving according to USP<786>.

Also, the present invention relate to a letrozole composition comprising a sterile biodegradable thermoplastic polymer of polylactic acid (PLA), wherein said PLA is milled and has a particle size volume distribution with a D90 not above 330 microns, preferably not above 280 microns when measured by laser diffraction analysis and with a D80 not below 135 microns when measured by laser diffraction analysis.

Also, the present invention relate to a letrozole composition comprising a sterile biodegradable thermoplastic polymer of polylactic acid (PLA), wherein said PLA is milled and has a particle size and/or said PLA has a particle size volume distribution with a D80 not below 135 microns when measured by laser diffraction analysis.

In a first aspect, the present invention relates to a stable sustained release letrozole composition for intramuscular administration suitable for forming an *in situ* intramuscular implant comprising from 10 to 500 mg of letrozole and a sterile biodegradable

thermoplastic polymer of polylactic acid (PLA), wherein said PLA is milled; and/or wherein said PLA has a particle size mass distribution with not more than 10% above 300 microns, preferably not above 250 microns, when measured by analytical sieving according to USP<786> and/or said PLA has a particle size volume distribution with a D90 not above 330 microns, preferably not above 280 microns when measured by laser diffraction analysis; and/or wherein said PLA has a particle size mass distribution where not more than 80 % of the particles have a particle size below 125 microns, when measured by analytical sieving according to USP<786> and/or said PLA has a particle size volume distribution with a D80 not below 135 microns when measured by laser diffraction analysis; and wherein the release of the active agent from the implant is between 2 and 30 % of the active agent each 28 days, preferably is between 5 and 25 % of the active agent each 28 days; and/or wherein the composition releases from 0.1 to 2 milligrams of letrozole every day, preferably from 0.13 to 0.80 milligrams of letrozole every day.

In a preferred embodiment, the composition comprises a water miscible solvent, preferably the solvent is dimethyl sulfoxide (DMSO).

The term "stable" as used herein refers to a pharmaceutical composition comprising letrozole wherein the total content of impurities originating from the decomposition of letrozole does not exceed 5 % area, preferably 3 % area, more preferably 2 % area and most preferably 1 % area determined by liquid chromatography (HPLC) at 230 nm if such a composition is stored for 2 months at 40 °C and 75 % relative humidity (RH).

When the PLA particle size is measured by analytical sieving according to USP<786>, the amplitude is 0.65 mm and the shaking time is 5 minutes. When the PLA particle size is measured by laser diffraction analysis, the particle size is determined by wet dispersion method. No sample pre-treatment was applied. The sample was directly added into the dispersion medium (water). Dispersion mechanism was stirring at 3000 rpm. In a preferred embodiment, the stable sustained release letrozole composition of the first aspect is characterized in that said composition releases up to 30 % of the letrozole in 30 days, preferably up to 25 % of the letrozole in 30 days; or up to 50 % of the letrozole in 100 days, preferably in 120 days and more preferably in 130 days; or said composition releases up to 80 % of the letrozole in 140 days, preferably in 180 days, more preferably in 200 days; or composition releases up to 80 % of the letrozole in 240 days, in an *in vitro* dissolution test performed with horizontal orbital motion at 50 rpm; medium: PBS pH 7.4; temperature: 37 ± 0.5 ºC; analytical technique: HPLC/UV; wavelength 230 nm.

In a preferred embodiment, the composition comprises from 10 to 450 mg of letrozole. In a preferred embodiment, the composition comprises from 30 to 90 mg of letrozole. In a preferred embodiment, the composition comprises from 80 to 150 mg of letrozole. In a preferred embodiment, the composition comprises from 150 to 250 mg of letrozole. In a preferred embodiment, the composition comprises from 350 to 450 mg of letrozole.

The term "active ingredient" or "active agent" refers to a therapeutically active compound, as well as any prodrugs thereof and pharmaceutically acceptable salts, hydrates and solvates of the compound and the prodrugs. In the present invention, the active agent is letrozole.

In a preferred embodiment, the end group of the PLA is an ester group.

In a preferred embodiment, the particle size of letrozole is such that less than 10 % of the particles have a size below 20 microns, less than 10 % of the particles have a size greater than 350 microns and the D50 is between 70-200 microns, when measured by laser diffraction analysis (volume distribution).

In a preferred embodiment, the composition comprises 5-40 wt. % letrozole, 20-40 wt. % PLA, 20-80 wt. % DMSO, in respect of the total weight of the composition before administration. Preferably, the composition comprises 15-35 wt. % letrozole, 25-35 wt. % PLA and 30-60 wt. % DMSO, in respect of the total weight of the composition before administration. Preferably, the composition comprises 18-28 wt. % letrozole, 30-35 wt. % PLA and 37-52 wt. % DMSO, in respect of the total weight of the composition before administration.

A preferred embodiment of the first aspect of the invention relates to a stable sustained release letrozole composition for intramuscular administration suitable for forming an *in situ* intramuscular implant comprising, preferably consisting essentially of, preferably consisting of: from 30 to 90 mg of letrozole, DMSO and a sterile biodegradable PLA, wherein the end group of the PLA is an ester group, wherein said PLA has a particle size mass distribution with not more than 10 % above 300 microns, preferably not above 250 microns, when measured by analytical sieving according to USP<786> and wherein said PLA has a particle size mass distribution where not more than 80 % of the particles have a particle size below 125 microns, when measured by analytical sieving according to USP<786> and wherein the release of the active agent from the implant is between 2 and 30 % of the active agent each 28 days, preferably is between 5 and 25 % of the active agent each 28 days; and wherein the particle size of letrozole is such that less

than 10 % of the particles have a size below 20 microns, less tan 10 % of the particles have a size greater than 350 microns and the D50 is between 70-200 microns, when measured by laser diffraction analysis (volume distribution); and wherein the composition comprises 15-35 wt. % letrozole, 25-35 wt. % PLA and 30-60 wt. % DMSO, in respect of the total weight of the composition before administration; and wherein the composition releases from 0.1 to 2 milligrams of letrozole every day; and wherein the stable sustained release composition provides a plasma level of letrozole between 1 and 40 ng/ml after 2 days from the implant administration.

A preferred embodiment of the first aspect of the invention relates to a stable sustained release letrozole composition for intramuscular administration suitable for forming an *in situ* intramuscular implant comprising, preferably consisting essentially of, preferably consisting of: from 80 to 150 mg of letrozole, DMSO and a sterile biodegradable PLA, wherein the end group of the PLA is an ester group, wherein said PLA has a particle size mass distribution with not more than 10% above 300 microns, preferably not above 250 microns, when measured by analytical sieving according to USP<786> and wherein said PLA has a particle size mass distribution where not more than 80 % of the particles have a particle size below 125 microns, when measured by analytical sieving according to USP<786> and wherein the release of the active agent from the implant is between 2 and 30 % of the active agent each 28 days, preferably is between 5 and 25 % of the active agent each 28 days; and wherein the particle size of letrozole is such that less than 10 % of the particles have a size below 20 microns, less tan 10 % of the particles have a size greater than 350 microns and the D50 is between 70-200 microns, when measured by laser diffraction analysis (volume distribution); and wherein the composition comprises 15-35 wt. % letrozole, 25-35 wt. % PLA and 30-60 wt. % DMSO, in respect of the total weight of the composition before administration; and wherein the composition releases from 0.1 to 2 milligrams of letrozole every day; and wherein the stable sustained release composition provides a plasma level of letrozole between 1 and 40 ng/ml after 2 days from the implant administration.

A preferred embodiment of the first aspect of the invention relates to a stable sustained release letrozole composition for intramuscular administration suitable for forming an *in situ* intramuscular implant comprising, preferably consisting essentially of, preferably consisting of: from 150 to 250 mg of letrozole, DMSO and a sterile biodegradable PLA, wherein the end group of the PLA is an ester group, wherein said PLA has a particle size mass distribution with not more than 10% above 300 microns, preferably not above 250

microns, when measured by analytical sieving according to USP<786> and wherein said PLA has a particle size mass distribution where not more than 80 % of the particles have a particle size below 125 microns, when measured by analytical sieving according to USP<786> and wherein the release of the active agent from the implant is between 2 and 30 % of the active agent each 28 days, preferably is between 5 and 25 % of the active agent each 28 days; and wherein the particle size of letrozole is such that less than 10 % of the particles have a size below 20 microns, less tan 10 % of the particles have a size greater than 350 microns and the D50 is between 70-200 microns, when measured by laser diffraction analysis (volume distribution); and wherein the composition comprises 15-35 wt. % letrozole, 25-35 wt. % PLA and 30-60 wt. % DMSO, in respect of the total weight of the composition before administration; and wherein the composition releases from 0.1 to 2 milligrams of letrozole every day; and wherein the stable sustained release composition provides a plasma level of letrozole between 1 and 40 ng/ml after 2 days from the implant administration.

A preferred embodiment of the first aspect of the invention relates to a stable sustained release letrozole composition for intramuscular administration suitable for forming an *in situ* intramuscular implant comprising, preferably consisting essentially of, preferably consisting of: from 350 to 450 mg of letrozole, DMSO and a sterile biodegradable PLA, wherein the end group of the PLA is an ester group, wherein said PLA has a particle size mass distribution with not more than 10 % above 300 microns, preferably not above 250 microns, when measured by analytical sieving according to USP<786> and wherein said PLA has a particle size mass distribution where not more than 80 % of the particles have a particle size below 125 microns, when measured by analytical sieving according to USP<786> and wherein the release of the active agent from the implant is between 2 and 30 % of the active agent each 28 days, preferably is between 5 and 25 % of the active agent each 28 days; and wherein the particle size of letrozole is such that less than 10 % of the particles have a size below 20 microns, less tan 10 % of the particles have a size greater than 350 microns and the D50 is between 70-200 microns, when measured by laser diffraction analysis (volume distribution); and wherein the composition comprises 15-35 wt. % letrozole, 25-35 wt. % PLA and 30-60 wt. % DMSO, in respect of the total weight of the composition before administration; and wherein the composition releases from 0.1 to 2 milligrams of letrozole every day; and wherein the stable sustained release composition provides a plasma level of letrozole between 1 and 40 ng/ml after 2 days from the implant administration.

In a preferred embodiment, the letrozole and the PLA are in a first component (first syringe) of the composition and the solvent is a separate component (second syringe) of the composition.

In another aspect, the present invention relates to a kit suitable for the *in situ* preparation of the composition of the first aspect, comprising two containers or syringes, wherein the first container or syringe comprises the letrozole and the PLA and the second container or syringe comprises the solvent, preferably DMSO.

In a second aspect, the present invention relates to a process for preparing the stable sustained release letrozole composition of the first aspect, comprising mixing the components of the composition up to 15 minutes prior to administration, preferably 10 minutes prior to administration, more preferably 5 minutes prior to administration. In a preferred embodiment, active ingredient and PLA are delivered already mixed.

In a preferred embodiment, the composition after preparation is a suspension. Preferably, the drug is in suspension and the PLA is dissolved in the solvent.

In a preferred embodiment, the composition is prepared by mixing the solvent, preferably DMSO with a previous solid mix of letrozole and PLA. In a preferred embodiment of the third aspect, the composition is prepared (reconstituted) by first by mixing the active agent with the PLA and then adding the solvent.

In a third aspect, the present invention relates to the use of the stable sustained release composition of the first aspect for administering a patient in need thereof from 0.1-2 milligrams of letrozole every day.

In a preferred embodiment, the stable sustained release composition of the first aspect is used for administering a patient in need thereof from 0.1-1.25 milligrams (mg) of letrozole every day. Preferably, the stable sustained release composition of the first aspect is used for administering a patient in need thereof from 0.1 to 1.20 mg, preferably from 0.13 to 1.15 mg, more preferably from 0.13 to 1.10 mg, even more preferably from 0.13 to 0.8 mg of letrozole every day.

In a preferred embodiment, the stable sustained release composition of the first aspect provides a plasma level of letrozole between 1 and 40 ng/ml after 2 days from the implant administration. Preferably, the stable sustained release composition of the first aspect provides a plasma level of letrozole between 1 and 40 ng/ml after 2 days from the implant

administration and continuously for at least six months, or from 6 to 12 months, or at least 12 months.

In a preferred embodiment, the stable sustained release composition of the first aspect provides a plasma level of letrozole between 1.5 and 30 ng/ml after 2 days from the implant administration. Preferably, the stable sustained release composition of the first aspect provides a plasma level of letrozole between 1.5 and 30 ng/ml after 2 days from the implant administration and continuously for at least six months, or from 6 to 12 months, or at least 12 months.

In a preferred embodiment, the stable sustained release composition of the first aspect provides a plasma level of letrozole between 1.5 and 25 ng/ml after 2 days from the implant administration. Preferably, the stable sustained release composition of the first aspect provides a plasma level of letrozole between 1.5 and 25 ng/ml after 2 days from the implant administration and continuously for at least six months, or from 6 to 12 months, or at least 12 months.

In a preferred embodiment, the stable sustained release composition of the first aspect provides a plasma level of letrozole between 1.5 and 20 ng/ml after 2 days from the implant administration. Preferably, the stable sustained release composition of the first aspect provides a plasma level of letrozole between 1.5 and 20 ng/ml after 2 days from the implant administration and continuously for at least six months, or from 6 to 12 months, or at least 12 months.

In a preferred embodiment, the stable sustained release composition of the first aspect provides a plasma level of letrozole between 1.5 and 15 ng/ml after 2 days from the implant administration. Preferably, the stable sustained release composition of the first aspect provides a plasma level of letrozole between 1.5 and 15 ng/ml after 2 days from the implant administration and continuously for at least six months, or from 6 to 12 months, or at least 12 months.

In a preferred embodiment, the stable sustained release composition of the first aspect provides a plasma level of letrozole between 1.5 and 10 ng/ml after 2 days from the implant administration. Preferably, the stable sustained release composition of the first aspect provides a plasma level of letrozole between 1.5 and 10 ng/ml after 2 days from the implant administration and continuously for at least six months, or from 6 to 12 months, or at least 12 months.

In a preferred embodiment, the stable sustained release composition of the first aspect is used for suppressing estradiol plasma levels to less than 1 pg/ml after 4 days from the implant administration.

In a preferred embodiment, the stable sustained release composition of the first aspect releases the drug with an immediate onset of action and continuously for at least 1 month, preferably at least 3 months, more preferably at least 6 months, even more preferably at least 12 months. In a preferred embodiment, the stable sustained release composition of the first aspect releases the drug with an immediate onset of action and continuously between 1 and 12 months or between 9 and 12 months, more preferably between 1 and 10 months, even more preferably between 1 and 6 months.

The expression "immediate onset of action" as used herein means that the estrogen plasma level suppression achieved by the composition of the invention is at least as early as the one achieved by oral therapy with Femara®, namely at day 4, no estradiol (E2) can be detected (see figures 1, 6 and 7).

In a preferred embodiment, the stable sustained release composition of the first aspect releases the drug with an immediate onset of action and continuously between 3 and 6 months.

In a preferred embodiment, the stable sustained release composition of the first aspect is an injectable intramuscular depot and sterile composition suitable for forming an *in situ* solid, semisolid or a gel implant in a body.

The compositions of the invention are preferably used in humans.

In another aspect, the present invention relates to the use of a letrozole composition suitable for forming an *in situ* intramuscular implant comprising a sterile biodegradable thermoplastic polymer of polylactic acid (PLA), for administering a patient in need thereof from 0.1-2 milligrams every day. Preferably, the use is for administering a patient in need thereof from 0.13-1.25 milligrams every day.

In a preferred embodiment, the composition provides a plasma level of letrozole between 1 and 40 ng/ml after 2 days from the implant administration. More preferably, the composition provides a plasma level of letrozole between 1.5 and 30 ng/ml after 2 days from the implant administration.

In a preferred embodiment of this aspect, the composition is used for suppressing estradiol plasma levels to less than 1 pg/ml after 4 days from the implant administration.

In a preferred embodiment of this aspect, the composition is used for aromatase inhibition, preferably in humans. In a preferred embodiment of this aspect, the composition is used for treating breast cancer. In a preferred embodiment of this aspect, the composition is used for adjuvant treatment of postmenopausal women with hormone receptor positive early breast cancer or for extended adjuvant treatment of postmenopausal women with early breast cancer who have received prior standard adjuvant tamoxifen therapy, or for first and second-line treatment of postmenopausal women with hormone receptor positive or unknown advanced breast cancer or any combination thereof.

Another aspect of the present invention relates to a letrozole composition for intramuscular administration comprising a sterile biodegradable thermoplastic polymer of polylactic acid (PLA), wherein the composition releases from 0.1-2 milligrams every day.

In a preferred embodiment of this aspect, the composition releases the drug with an immediate onset of action and continuously for at least 1 month, preferably at least 3 months, more preferably at least 6 months, even more preferably at least 12 months. In a preferred embodiment of this aspect, the composition releases the drug with an immediate onset of action and continuously for at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 7 months, at least 8 months, at least 9 months, at least 10 months, at least 11 months or at least 12 months. In a preferred embodiment, the composition releases the drug with an immediate onset of action and continuously for at least 12 months. In another preferred embodiment, the composition releases the drug with an immediate onset of action and continuously between 3 and 6 months.

In a preferred embodiment of this aspect, the composition is an injectable intramuscular depot and sterile composition suitable for forming an *in situ* solid, semisolid or a gel implant in a body.

The present invention relates to a letrozole composition suitable for forming an *in situ* intramuscular implant which can maintain the required letrozole plasma levels for hormone suppression during at least 6 months.

This long-term sustained hormone suppression therapy has been shown to provide a superior clinical outcome in human compared to oral daily dosage treatment.

Also, sustained lower effective letrozole plasma level with lower doses (compared to oral treatment) reduce the adverse side effects (bone mass loss, bone/joint/muscle pain, dyslipidemia) due to lower exposure to drug. Moreover, the present invention provides a better safety profile which positively impact treatment duration adherence.

CLAUSES

1.- Use of a letrozole composition suitable for forming an *in situ* intramuscular implant comprising a sterile biodegradable thermoplastic polymer of polylactic acid (PLA), for administering a patient in need thereof from 0.1-2 milligrams every day.

2.- The use according to the preceding clause, for administering a patient in need thereof from 0.1-1.25 milligrams every day.

3.- The use according to any one of the preceding clauses, wherein the composition provides a plasma level of letrozole between 1 and 40 ng/ml after 2 days from the implant administration.

4.- The use according to any one of the preceding clauses, between 1.5 and 30 ng/ml after 2 days from the implant administration.

5.- The use according to any one of the preceding clauses for suppressing estradiol plasma levels to less than 1 pg/ml after 4 days from the implant administration.

6.- A letrozole composition for intramuscular administration comprising a sterile biodegradable thermoplastic polymer of polylactic acid (PLA), wherein the composition releases from 0.1-2 milligrams every day.

7.- A letrozole composition for intramuscular administration comprising a sterile biodegradable thermoplastic polymer of polylactic acid (PLA) according to clause 6 wherein the composition releases the drug with an immediate onset of action and continuously for at least 1 month, preferably at least 3 months, more preferably at least 6 moths, even more preferably at least 12 months.

8.- A letrozole composition according to any one of the preceding clauses 6 or 7 wherein the composition releases the drug with an immediate onset of action and continuously between 3 and 6 months.

9.-. A letrozole composition according to any one of the preceding clauses 6 to 8 wherein the composition is an injectable intramuscular depot and sterile composition suitable for forming an *in situ* solid, semisolid or a gel implant in a body.

10.- A letrozole composition according to any one of the preceding clauses 6 to 9, wherein said PLA is milled; and/or wherein said PLA has a particle size mass distribution with not more than 10% above 300 microns, preferably not above 250 microns, when measured by analytical sieving according to USP<786> and/or with a D90 in volume not above 330 microns, preferably not above 280 microns when measured by laser diffraction analysis; and/or wherein said PLA has a particle size distribution where not more than 80 % in mass of the particles have a particle size below 125 microns, when measured by analytical sieving according to USP<786> and/or with a D80 in volume not below 135 microns when measured by laser diffraction analysis.

11.- A letrozole composition according to any one of the preceding clauses 6 to 10, characterized in that said composition releases up to 30 % of the letrozole in 30 days, preferably up to 25 % of the letrozole in 30 days; or up to 50 % of the letrozole in 100 days, preferably in 120 days and more preferably in 130 days; or said composition releases up to 80 % of the letrozole in 140 days, preferably in 180 days, more preferably in 200 days; or composition releases up to 80 % of the letrozole in 240 days, in an in vitro dissolution test performed with horizontal orbital motion at 50 rpm; medium: PBS pH 7.4.; temperature: 37 ± 0.5 ºC; analytical technique HPLC/UV; wavelength 230 nm.

DESCRIPTION OF THE FIGURES

The following figures are provided to help with the interpretation of the object of the present invention, but do not imply any limitation.

Figure 1. Rapid and sustained estradiol suppression with lower doses. Estradiol plasma levels (pg/ml) observed after administering Femara® or the composition of the invention.

Figure 2. Rapid and sustained letrozole plasma levels. Letrozole plasma levels (ng/ml) observed after administering Femara® or the composition of the invention.

Figure 3. Cumulative percentage of released letrozole in an *in vitro* dissolution test from a composition comprising a PLA with with a particle size mass distribution where more than 10 % of the particles have a particle size of 300 microns or more, when measured by analytical sieving according to USP<786>.

Figure 4. Cumulative percentage of released letrozole from a composition of the invention in an *in vitro* dissolution test.

Figure 5. Cumulative percentage of released letrozole in an *in vitro* dissolution test from a composition comprising a PLA with a particle size mass distribution where at least 80 % of the particles have a particle size of 125 microns or less, when measured by analytical sieving according to USP<786>.

Figure 6. Estradiol plasma levels (pg/ml) observed after administering Femara® or the composition of the invention of 50 mg letrozole.

Figure 7. Estradiol plasma levels (pg/ml) observed after administering Femara® or the composition of the invention of 100 mg letrozole.

Figure 8. Rapid and sustained letrozole mean plasma levels. Letrozole plasma levels (ng/ml) observed after administering Femara® or the compositions of the invention.

Figure 9. Particle size distribution of the PLA of the composition of the invention measured by laser diffraction analysis. Horizontal axis: particle size in micrometres. Vertical axis: volume (%), indicating the percentage of particles with the corresponding particle size, measured by laser diffraction by wet dispersion method in water and dispersing by stirring at 3000 rpm.

EXAMPLES

The following examples are illustrative of the invention and are not to be considered limiting.

Example 1: Compositions

The following formulations are prepared:

A ready-to-use formulation can be prepared, for example, and included in a syringe ready for use for intramuscular injection. The same formulation may form part, for example, of a kit of two syringes, one male and one female or two male syringes linked by a connector in which the solution of PLA in DMSO is in one syringe and the letrozole is in solid form in a second syringe. Similarly, the final composition can be obtained by, for example, maintaining one syringe with the PLA and letrozole in solid state and the solvent (DMSO) in a second syringe.

Formulation 1:

Ingredient	Amount (mg, % wt)
Lactic acid polymer (ester terminal group) of intrinsic viscosity of 0.3 dl/g, irradiated as raw material at 10 kGy.	55.20 (35.8%)
Dimethyl sulfoxide	82.80 (53.7%)
Letrozole	16.20 (10.5%)

Formulation 2: formulation with letrozole in suspension

Ingredient	Amount (mg, % wt)
Lactic acid polymer (ester terminal group) of intrinsic viscosity of 0.3 dl/g, irradiated as raw material at 10 kGy.	38.80 (30%)
Dimethyl sulfoxide	58.30 (45%)
Letrozole	32.40 (25%)

Letrozole particle size in formulation 2 was characterized by the technique of laser ray diffraction (Malvern Mastersizer 2000, suspended in water until obscuration of 9.41%) and had the following distribution (in % volume): d(0.1) = 38.21 µm, d(0.5) = 141.35 µm and d(0.9) = 312.13 µm.

Formulation 3:

Ingredient	Amount (mg)
Lactic acid polymer (carboxylic terminal group) of intrinsic viscosity of 0.3 dl/g, irradiated as raw material at 10 kGy.	38.80
Dimethyl sulfoxide	58.30
Letrozole	32.40

Formulation 4:

Ingredient	Amount (mg)
Lactic acid polymer (ester terminal group) of intrinsic viscosity of 0.3 dl/g, irradiated as raw material at 10 kGy.	38.80
Dimethyl sulfoxide	58.30
Letrozole	32.40

Formulation 5:

Ingredient	Amount (mg, % wt)
Lactic acid polymer (carboxylic terminal group) of intrinsic viscosity of 0.3 dl/g, irradiated as raw material at 10 kGy.	107.6 (31.1%)
Dimethyl sulfoxide	151.7 (43.9%)
Letrozole	86.5 (25%)

Formulation 6:

Ingredient	Amount (mg)
Lactic acid polymer (ester terminal group) of intrinsic viscosity of 0.3 dl/g, irradiated as raw material at 10 kGy.	107.6
Dimethyl sulfoxide	151.7
Letrozole	86.5

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Formulations 7 to 12:

Formulation	7	8	9	10	11	12
Ingredient	Amount (% wt)	Amount (% wt)	Amount (% wt)	Amount (% wt)	Amount (% wt)	Amount (% wt)
Lactic acid polymer (PLA) terminating in a carboxylic group	28-36	15-42.5	29.6-32.7			
Lactic acid polymer (PLA) ester terminal group				15-42.5	28-36	29.6-32.7
Dimethyl sulfoxide	38.5-52	25-59.5	42.2-45.6	25-59.5	38.5-52	42.2-45.6
Letrozole	20-30	15-50	24-26	15-50	20-30	24-26

For preferred compositions, the % w/w in the composition of the active agent was between 20.0 and 27.0 %. The % w/w in the composition of the PLA was between 20.0 and 50.0 %. The % w/w in the composition of the solvent was between 23.0 and 60.0 %. The compositions were mixed in a syringe to form suitable implants.

Different types of PLA were used for these compositions:

1. PLA with particle size mass distribution where more than 10 % of the particles had a particle size of 300 microns or above when measured by analytical sieving according to USP<786>;
2. PLA with particle size volume distribution with D90 above 330 microns when measured by laser diffraction analysis;
3. PLA with particle size mass distribution where no more than 10 % of the particles had a particle size above 300 microns and no more than 80 % of the particles have a particle size below 125 microns when measured by analytical sieving according to USP<786>;
4. PLA with particle size volume distribution with D90 not above 330 microns and D80 not below 135 microns when measured by laser diffraction analysis;
5. PLA with particle size mass distribution where more than 80 % of the particles have a particle size below 125 microns, when measured by analytical sieving according to USP<786>;

6. PLA with particle size volume distribution with D80 below 135 microns when measured by laser diffraction analysis.

Compositions of the invention were prepared first by dry mixing the active agent with the PLA and then adding the solvent, preferably DMSO to dissolve the PLA and have a suspension of the active agent. The reconstitution process is to be carried out immediately prior to injection, and the time for preparation does not exceed 15 minutes, preferably 10 minutes, more preferably 5 minutes, before the IM composition is administered.

The implants prepared this way were used for the following dissolution test: horizontal orbital motion at 50 rpm; medium: PBS pH 7.4.; temperature: 37 ± 0.5 ºC; analytical technique HPLC/UV; wavelength 230 nm.

It was observed that for PLAs 1 and 2, the release was not as satisfactory sustained as desired when preferred time of preparation was applied (Fig. 3). The PLA used in the composition of figure 3 had a particle size mass distribution where 18.1 % of the particles were bigger than 300 microns and 28.3 % of the particles were smaller than 125 microns, measured by analytical sieving according to USP<786>. Said PLA had a particle size volume distribution with a D90 of 421 microns and a D80 of 324 microns when measured by laser diffraction analysis.

However, for PLAs 3 and 4, the sustained release was satisfactory (Fig. 4). The PLA used in the composition of figure 4 had a particle size mass distribution where 0.8 % of the particles were bigger than 300 microns and 58.5 % of the particles were smaller than 125 microns, measured by analytical sieving according to USP<786>. Said PLA had a particle size volume distribution with a D90 of 214 microns and a D80 of 170 microns when measured by laser diffraction analysis.

When PLAs 5 and 6 were used, big and hard agglomerates formed, and the composition could not be prepared within the preferred time of no more than 15 minutes. Thus, this composition was not considered clinically suitable. In any case, the implant was assayed, and sustained release resulted satisfactory (Fig 5). The PLA used in the composition of figure 5 had a particle size mass distribution where 1.6 % of the particles were bigger than 300 microns and 88.8 % of the particles were smaller than 125 microns, measured by analytical sieving according to USP<786>. Said PLA had a particle size volume distribution with a D90 of 155 microns and a D80 of 124 microns when measured by laser diffraction analysis.

Particle size determination

Analytical sieving according to USP<786>

The PLA particle size mass distribution was determined by sieve stack technique using the following sizes: 425 > 355 > 300 > 250 > 212 > 180 > 150 > 125 > 106 > 75. The amplitude was 0.65 mm and the shaking time 5 minutes.

Laser light diffraction

The PLA particle size distribution is expressed as volume distribution and was determined by laser diffraction technique by wet dispersion method. No sample pre-treatment was applied. The sample was directly added into the dispersion medium (water). Dispersion mechanism was stirring at 3000 rpm and the sample was stabilized for 30 seconds before measuring.

Preliminary Phase I results

Preliminary results suggest that sustained long-term hormone suppression therapy (HT) may obtain a superior clinical outcome in breast cancer compared to an oral daily dosage treatment.

Early discontinuation and non-adherence to HT are common and associated with increased mortality – improved treatment compliance with Letrozole ISM® has potential to enhance treatment.

Sustained lower effective doses (compared to oral treatment) could reduce adverse side effects (bone mass loss, bone/joint/muscle pain, dyslipidemia) due to lower exposure to drug.

Better safety profile has potential to positively impact treatment duration adherence.

Phase I results

This is a Phase I, open label, dose escalation study designed to evaluate the pharmacokinetics, safety, and tolerability of single intramuscular injections of Letrozole ISM at different strengths in approximately 120 voluntary healthy post menopausal women. The study has four arms:

Experimental: Cohort 1: Letrozole ISM 50 mg: 14 oral doses of 2.5 mg Femara® (once daily) + single IM injection of 50 mg Letrozole ISM.

Experimental: Cohort 2: Letrozole ISM 100 mg: 14 oral doses of 2.5 mg Femara® (once daily) + single IM injection of 100 mg Letrozole ISM.

Experimental: Cohort 3: Letrozole ISM 200 mg: 14 oral doses of 2.5 mg Femara® (once daily) + single IM injection of 200 mg Letrozole ISM.

Experimental: Cohort 4: Letrozole ISM 400 mg: 14 oral doses of 2.5 mg Femara® (once daily) + single IM injection of 400 mg Letrozole ISM.

The objective of this study is to assess the pharmacokinetic profile of a single ascending doses of Letrozole ISM, and secondly, to evaluate safety and tolerability of single ascending doses of Letrozole ISM, measure estrogen levels, and characterize oral letrozole pharmacokinetic profile to be used in subsequent comparison to Letrozole ISM.

The study is carried out in healthy post-menopausal women who satisfy inclusion and exclusion criteria. The study design includes a screening period and 2 treatment periods. Treatment Period 1 comprises of 14 oral dose administrations of 2.5 mg Femara®. Treatment Period 2 comprises of a single IM dose of 50, 100, 200 and 400 mg Letrozole ISM. The total planned study duration is 71 weeks, approximately.

The inclusion/exclusion criteria for the 120 participants are the following:

Inclusion Criteria:

Healthy post-menopausal women, ≥ 18 and ≤ 75 years of age, who have achieved complete menopause, either natural or surgical, and amenorrhea, and have not been on hormone replacement therapy in the last 3 months.

Post-menopausal subjects should have absence of menses for 1 year, and oophorectomized subjects should have absence of menses for at least 6 weeks. For oophorectomized subjects and subjects who have had a hysterectomy, a surgical pathology report documenting the absence of malignant disease is required. In addition, for oophorectomized subjects an operative report documenting bilateral oophorectomy is required.

Baseline follicle-stimulating hormone (FSH) and 17β-estradiol plasma levels should be consistent with the post-menopausal status of the subject (FSH ≥ 40 mIU/mL; 17β-estradiol ≤ 31 pg/mL), confirmed at least 48 hours prior to dosing.

Weight of ≥ 50 kg and a BMI ≥ 19 and ≤ 39 kg/m2.

Subjects will be in good health, as determined by medical history, physical examination, vital signs assessments (pulse rate, systolic and diastolic blood pressure, and temperature), clinical laboratory evaluations, and 12-lead ECG. Minor deviations outside the reference ranges will be acceptable, if deemed not clinically significant by the investigator.

Subjects who have not had a mammogram within the last 12 months (documentation required) must be willing to have one performed.

Subjects with an intact uterus and cervix who have not had a Papanicolaou (pap) smear test within the last 6 months (documentation required) must be willing to have one performed.

Subjects will have given their written informed consent to participate in the study and to abide by the study restrictions.

Subjects should be able to communicate with clinic staff.

Exclusion Criteria:

Subjects who have a history of allergy or hypersensitivity to letrozole or any of the inactive ingredients in the last 3 months.

Subjects who have a history of galactose intolerance, severe hereditary lactase deficiency glucose-galactose malabsorption.

Subjects who have used estrogen or progesterone hormone replacement therapy, thyroid replacement therapy, oral contraceptives, androgens, luteinizing hormone (LH) releasing hormone analogs, prolactin inhibitors, or antiandrogens within 3 months prior to Screening.

Subjects who have regularly taken foods or food supplements that contain high levels of Isoflavinoids, including soybean, soymilk, soynuts, chickpeas, alfalfa, fava beans, kudzu, miso and tofu in the 14 days prior to dosing (Treatment Period 1).

The investigator and medical monitor will determine on a case-by-case basis if a subject who intakes food or food supplements containing Isoflavinoids is eligible to participate in the study.

Subjects who have used:

Any medications including St. John's wort, known to be potent or moderate inducers of CYP P450 3A4 in the 3 weeks prior to dosing (Treatment Period 1).

Any medications or products known to be potent or moderate inhibitors of CYP P450 3A4 (e.g. grapefruit juice) in the 7 days prior to dosing on Treatment Period 1.

Any prescribed preparations within 14 days prior to dosing (Treatment Period 1), unless in the opinion of the investigator (or designee) the medication will not interfere with the study procedures or compromise safety.

Any non-prescribed systemic or topical medications within 7 days of dosing (Treatment Period 1) unless in the opinion of the investigator (or designee) the medication will not interfere with the study procedures or compromise safety. Vitamins and minerals including the use of calcium and/or vitamin D for osteoporosis prevention are allowed.

Subjects who have been diagnosed with osteoporosis (previously or results from screening DEXA for this study with a T score < -2.5). Subjects with osteopenia (with the T-score between -1 and -2.5) will be allowed to participate in this study.

Subjects who are not on a stable dose of long- or short-acting bisphosphonates therapy for at least 3 months prior to Screening.

Subjects who are on raloxifene therapy.

Subjects who have an abnormality in heart rate, blood pressure, or temperature at Screening and prior to first dose (Treatment Period 1) that in the opinion of the investigator increases the risk of participating in the study. Resting SBP must be ≤ 150mmHg and resting DBP ≤ 95 mmHg.

Subjects who have an abnormality in the 12-lead ECG at Screening and prior to first dose (Treatment Period 1) that in the opinion of the Investigator increases the risk of participating in the study.

Subjects who have any clinically significant abnormal physical examination finding.

Subjects who have any clinically significant abnormal laboratory safety findings at Screening or Check-in, upon repeat testing, as determined by the investigator (1 repeat assessment is acceptable).

Subjects who have ALT or AST >1.5 × ULN. For subjects with elevated total bilirubin, direct and indirect bilirubin will be evaluated.

Subjects with elevated cholesterol or triglyceride levels above the ULN must be determined by the Investigator to be not clinically significant.

Subjects who have relevant diseases or clinically significant abnormal relevant findings at Screening, as determined by medical history, physical examination, laboratory, ECG, DEXA, and breast and pelvic examination.

Subjects who have history of any significant chronic disease, such as but not limited to: thrombotic disorders, coronary artery or cerebrovascular disease, liver, kidney or gallbladder dysfunction/disorder(s), diabetes or any other endocrine disease, estrogen dependent neoplasia, post-menopausal uterine bleeding, or endometrial hyperplasia. Subjects with cholecystectomy will be permitted if no medical sequelae post-surgery.

History of cancer within the past 5 years with the exception of non-melanoma skin cancer.

Subjects who have a history of drug-dependence, and recent history of alcoholism or abuse of alcohol.

Subjects who have a positive result for hepatitis B surface antigen (HBsAg), hepatitis B core antibody, hepatitis C antibody, or human immunodeficiency virus (HIV) antibodies.

Subjects with a positive drugs of abuse screen or alcohol breath test at Screening (urine will be screened for the presence of the following: amphetamine, barbiturates, benzodiazepines, cannabinoid, cocaine, opiates, phencyclidine, and methadone).

Subjects with a history of, or difficulty of, access to veins for venipuncture.

Subjects who have donated blood in the 30 days prior to first dose (Treatment Period 1).

Subjects who have received blood products within 2 months prior to Screening.

Subjects who have received a drug in research or have participated in other clinical trials within 30 days, or 5 half-lives (whichever is longer) prior to dosing (Treatment Period 1).

Subjects who have previously taken part in or have withdrawn from this study. (Subjects who have been screened for but not included in a cohort or subjects who dropped out

from screening in a previous cohort for non-medical reasons may be eligible to be included in subsequent cohorts.)

Any other unspecified reason that, in the opinion of the investigator (or designee) or Sponsor, makes the subject unsuitable for enrollment.

PK results

Letrozole plasma concentrations have been analyzed up to Day 393 and Day 225 following a single intramuscular (IM) injection of Letrozole ISM 50 mg and 100 mg, respectively. The majority of subjects had sustained quantifiable letrozole plasma concentrations up to the last sampling time points reported in both groups (Figure 8). Dose-normalized peak exposure (Cmax/D) is comparable between both dose strength of Letrozole ISM.

Letrozole mean maximum exposure concentrations observed for Femara® at steady state (2.5 mg QD for 14 days) were approximately 12 and 8 fold the one observed for Letrozole 50 mg and 100 mg, respectively.

Plasma estrogen levels decreased rapidly from baseline following administration of letrozole. The hormones decreased to stable levels below 1 pg/mL at approximately 4 days post-Femara®/Letrozole ISM treatment (Figs. 6 and 7). The sustained suppression of estrogen levels were maintained for up to 281 days and 197 days for Letrozole ISM 50 mg and 100 mg, respectively. There were no apparent differences in the extent of hormonal level decrease between Letrozole ISM 50 mg and 100 mg.

CLAIMS

1.- A stable sustained release letrozole composition for intramuscular administration suitable for forming an *in situ* intramuscular implant comprising from 10 to 500 mg of letrozole and a sterile biodegradable thermoplastic polymer of poly(lactic acid) (PLA), wherein said PLA is milled; and/or wherein said PLA has a particle size mass distribution with not more than 10% above 300 microns, preferably not above 250 microns, when measured by analytical sieving according to USP<786> and/or said PLA has a particle size volume distribution with a D90 not above 330 microns, preferably not above 280 microns when measured by laser diffraction analysis; and/or wherein said PLA has a particle size mass distribution where not more than 80 % of the particles have a particle size below 125 microns, when measured by analytical sieving according to USP<786> and/or said PLA has a particle size volume distribution with a D80 not below 135 microns when measured by laser diffraction analysis; and wherein the release of the active agent from the implant is between 2 and 30 % of the active agent each 28 days, preferably is between 5 and 25 % of the active agent each 28 days; and/or wherein the composition releases from 0.1 to 2 milligrams of letrozole every day, preferably from 0.13 to 0.80 milligrams of letrozole every day.

2.- The stable sustained release letrozole composition according to the preceding claim, characterized in that said composition releases up to 30 % of the letrozole in 30 days, preferably up to 25 % of the letrozole in 30 days; or up to 50 % of the letrozole in 100 days, preferably in 120 days and more preferably in 130 days; or said composition releases up to 80 % of the letrozole in 140 days, preferably in 180 days, more preferably in 200 days; or composition releases up to 80 % of the letrozole in 240 days, in an *in vitro* dissolution test performed with horizontal orbital motion at 50 rpm; medium: PBS pH 7.4.; temperature: 37 ± 0.5 ºC; analytical technique HPLC/UV; wavelength 230 nm.

3.- The stable sustained release composition according to any one of the preceding claims, wherein the composition releases the drug with an immediate onset of action and continuously for at least 1 month, preferably at least 3 months, more preferably at least 6 moths, even more preferably at least 12 months.

4- The stable sustained release composition according to any one of the preceding claims, wherein the composition releases the drug with an immediate onset of action and continuously between 3 and 6 months.

5.-. The stable sustained release composition according to any one of the preceding claims, wherein the composition is an injectable intramuscular depot and sterile composition suitable for forming an *in situ* solid, semisolid or a gel implant in a body.

6. A process for preparing the stable sustained release letrozole composition of any one of the preceding claims, comprising mixing the components of the composition up to 15 minutes prior to administration, preferably 10 minutes prior to administration, more preferably 5 minutes prior to administration.

7.- The process according to the preceding claim, wherein the composition is prepared by mixing the solvent with a previous solid mix of letrozole and PLA.

8.- The stable sustained release composition of any one of claims 1 to 5, for use in administering a patient in need thereof from 0.1-2 milligrams of letrozole every day.

9. The stable sustained release composition for use according to the preceding claim, for administering a patient in need thereof from 0.13-0.8 milligrams of letrozole every day.

10.- The stable sustained release composition for use according to any one of the two preceding claims, wherein the composition provides a plasma level of letrozole between 1 and 40 ng/ml after 2 days from the implant administration.

11.- The stable sustained release composition for use according to any one of the three preceding claims, wherein the composition provides a plasma level of letrozole between 1.5 and 30 ng/ml after 2 days from the implant administration.

12.- The stable sustained release composition for use according to any one of the four preceding claims, for suppressing estradiol plasma levels to less than 1 pg/ml after 4 days from the implant administration.

13.- The stable sustained release composition for use according to any one of the five preceding claims, for aromatase inhibition, preferably in humans.

14.- The stable sustained release composition for use according to any one of the six preceding claims, for treating breast cancer.

15.- The stable sustained release composition for use according to any one of the seven preceding claims, for adjuvant treatment of postmenopausal women with hormone

receptor positive early breast cancer or for extended adjuvant treatment of postmenopausal women with early breast cancer who have received prior standard adjuvant tamoxifen therapy, or for first and second-line treatment of postmenopausal women with hormone receptor positive or unknown advanced breast cancer.

16.- A kit suitable for the *in situ* preparation of the composition of any one of claims 1 to 5, comprising two containers or syringes, wherein the first container or syringe comprises the letrozole and the PLA and the second container or syringe comprises the solvent, preferably DMSO.