Title: IMPLANT COMPRISING A CORE AND A TUBE ENCASING THE CORE

Abstract: The present invention relates to an implant comprising: - a core material comprising polydimethylsiloxane or at least one hydrogel polymer; - a tube encasing said core material comprising an ethylene vinyl acetate polymer or at least one hydrogel polymer; - a sealant for closure of the open ends of said tube comprising polydimethylsiloxane or a mono-, di-, or tricetoxy derivative thereof, or at least one hydrogel polymer; and - at least one active ingredient; wherein said at least one active ingredient is selected from the group comprising celletex, sulfadiazine, ancestrofen, cestradiol, ethoxydiol acetate, leupropin, buserelin, gonadotropin, triptorelin, nafarelin, deslorelin, histrelin, and supreluna; and with the proviso that when the sealant is said at least one hydrogel polymer, the core material comprises polydimethylsiloxane. Furthermore, the invention relates to an implant for use as a medicament. In particular, the invention relates to an implant for use in the treatment of endometriosis.
IMPLANT COMPRISING A CORE AND A TUBE ENCASING THE CORE

FIELD OF THE INVENTION

The present invention relates to an implant of polymeric material. Furthermore, the invention relates to an implant for use as a medicament. In particular, the invention relates to an implant for use in the treatment of endometriosis.

BACKGROUND OF THE INVENTION

Endometriosis is a gynecological disorder characterized by the presence of endometrial tissue outside the endometrial cavity, most commonly in the abdominal cavity. The ectopic endometrial tissue remains hormone responsive, such as cyclical bleeding and estrogen-dependent growth. The ectopic growth triggers abdominal pain leading to a loss in quality of life, and immune system activation. Frequently, endometriosis leads to infertility in affected women. Because endometriosis is often confined to the peritoneal cavity, localized drug delivery into this cavity is of great interest for the treatment of endometriosis and in general for the treatment of pathologies confined to the peritoneal cavity.

Implants of polymeric material as drug delivery systems are known for some time. Implantable delivery systems of polymeric material are known for instance for the delivery of contraceptive agents. However, prior art implants do not sufficiently control drug release. Various devices have been proposed for solving this problem. However, none have been entirely satisfactory. For example, US Patent No. 6,117,441 discloses an implantable system for use as a male contraception and as a treatment of benign prostate hypertrophy and other conditions.

Accordingly, a need exists for improved polymeric implants. In particular, there remains a need for an implant with controlled drug release for use in the treatment of endometriosis. It is an object of the invention to provide an implant with controlled drug release.

SUMMARY OF THE INVENTION

In a first aspect, the present invention provides implants for extended release of an active ingredient, comprising a core material comprising polydimethylsiloxane (PDMS) or at least one hydrogel polymer; a tube encasing said core material comprising an ethylene vinyl acetate polymer or at least one hydrogel polymer; a sealant for closure of the open ends of said tube comprising polydimethylsiloxane or a mono-, di-, or triacetoxy derivative thereof, or at least one hydrogel polymer; and at least one active ingredient; with the proviso that when the sealant is said at least one hydrogel polymer, the core material comprises polydimethylsiloxane.
Preferably, the present invention provides an implant comprising: a core material comprising polydimethylsiloxane or at least one hydrogel polymer; a tube encasing said core material comprising an ethylene vinyl acetate polymer or at least one hydrogel polymer; a sealant for closure of the open ends of said tube comprising polydimethylsiloxane or a mono-, di-, or triacetoxy derivative thereof or at least one hydrogel polymer; and at least one active ingredient; with the proviso that when the sealant is said at least one hydrogel polymer, the core material comprises polydimethylsiloxane.

In an embodiment, the present invention provides an implant comprising: a core material comprising polydimethylsiloxane or at least one hydrogel polymer; a tube encasing said core material comprising an ethylene vinyl acetate polymer or at least one hydrogel polymer; a sealant for closure of the open ends of said tube comprising polydimethylsiloxane or a mono-, di-, or triacetoxy derivative thereof, or at least one hydrogel polymer; and at least one active ingredient; wherein said at least one active ingredient is selected from the group comprising celecoxib, sulindac, tamoxifen, oestrogen, oestradiol, ethinyl oestradiol, mestranol, dienogest, norgestrel, levonorgestrel, desogestrel, norgestimate, ethynodiol diacetate, leuprolelin, buserelin, gonrelin, triptorelin, nafarelin, deslorelin, histrelin, and supprelin; and with the proviso that when the sealant is said at least one hydrogel polymer, the core material comprises polydimethylsiloxane.

In a preferred embodiment, the present invention provides an implant comprising: a core material comprising polydimethylsiloxane; a tube encasing said core material comprising an ethylene vinyl acetate polymer; a sealant for closure of the open ends of said tube comprising polydimethylsiloxane or a mono-, di-, or triacetoxy derivative thereof; and at least one active ingredient; wherein said at least one active ingredient is selected from the group comprising celecoxib, sulindac, tamoxifen, oestrogen, oestradiol, ethinyl oestradiol, mestranol, dienogest, norgestrel, levonorgestrel, desogestrel, norgestimate, ethynodiol diacetate, leuprolelin, buserelin, gonrelin, triptorelin, nafarelin, deslorelin, histrelin.

The present inventors have found that an implant according to the invention has the advantage of overcoming one or more of the above-mentioned problems of the prior art.

The present implants of the invention have the advantage of allowing controlled liberation of active ingredients over extended periods of time and hence increase patient compliance during long-term treatment. Controlled drug release allows the sustained delivery of the drug in a predetermined amount and this during a defined period of time. Furthermore, the present implants protect their enclosed active ingredient from the physical environment, thereby improving active ingredient stability in vivo. Furthermore, in
an embodiment, the implant of the present invention can be easily localized in the body, due to the presence of a radiopaque material and/or an inert metal coating. This is advantageous at the time of implantation and after the treatment in order to facilitate the removal of the implant.

In a second aspect, the present invention relates to an implant for use as a medicament. In particular, the invention relates to an implant for use in the treatment of endometriosis. The use of implants of the present invention is advantageous because these implants allow efficient treatment while avoiding side effects, due to the sustained and localized delivery of a therapeutically effective amount of the enclosed drug. Furthermore, the use of implants of the present invention is advantageous because these implants allow treatment during longer periods, due to the controlled release of the active ingredient. The invention therefore also relates to an implant according to the invention for use as a medicament, wherein said implant is administered once per 180 days, or less frequently, preferably once per year, or less frequently. A further advantage of the use of the present implants is that these implants allow simultaneous delivery of several active ingredients of different therapeutic classes.

The present invention will now be further described. In the following passages, different aspects of the invention are defined in more detail. Each aspect so defined may be combined with any other aspect or aspects unless clearly indicated to the contrary. In particular, any feature indicated as being preferred or advantageous may be combined with any other feature or features indicated as being preferred or advantageous.

**BRIEF DESCRIPTION OF THE FIGURES**

Figures 1 and 2 represent X-ray images of implants comprising barium sulfate.

Figures 3, 4 and 5 represent X-ray images of in vivo implants comprising barium sulfate.

Figure 3A represents the front view of the animal on day 0. Figure 3B represents the side view of the animal on day 0. Figure 4A represents the front view of the animal on day 0. Figure 4B represent the side view of the animal on day 0. Figure 4C represents the front view of the animal after 2 months. Figure 4D represents the side view of the animal after 2 months. Figure 5A represents the front view of the animal on day 0. Figure 5B represents the side view of the animal on day 0.

Figure 6A represents a graph illustrating the mean release of anastrozole per 24h as a function of time for an implant without a sealant. Figure 6B represents a graph illustrating the mean release of anastrozole per 24h as a function of time for an implant with MED-2000 adhesive silicone as a sealant.
Figure 7 represents a graph illustrating the mean release of anastrozole per 24h as a function of time for sterilized and non-sterilized implants.

Figure 8A: represents a graph illustrating the mean release of celecoxib per 24h as a function of time for implants without a sealant and with an EVA (10% of VA) membrane of different thicknesses. Figure 8B: represents a graph illustrating the mean release of celecoxib per 24h as a function of time for implants with an EVA sealant and with an EVA (10% of VA) membrane of different thicknesses. Figure 8C: represents a graph illustrating the mean release of celecoxib per 24h as a function of time for implants with a PDMS sealant and with an EVA (10% of VA) membrane of different thicknesses.

Figure 9A represents a graph illustrating the mean release of celecoxib per 24h as a function of time for implants without a tube and with an EVA tube comprising 18% or 28% by weight of vinyl acetate. Figure 9B is a close-up view of figure 9A.

Figure 10A represents a graph illustrating the concentration of celecoxib in serum of rats as a function of the number of days after implantation. Figure 10B represents a graph illustrating the concentration of celecoxib in peritoneal liquid of rats as a function of the number of days after implantation.

Figure 11A represents a graph illustrating the concentration of anastrozole in serum of rats as a function of the number of days after intraperitoneal implantation. Figure 11B represents a graph illustrating the concentration of anastrozole in peritoneal fluid of rats as a function of the number of days after implantation.

Figure 12A represents a graph illustrating the concentration of celecoxib in serum of cynomolgus monkeys as a function of the number of days after implantation. Figure 12B represents a graph illustrating the concentration of anastrozole in serum of cynomolgus monkeys as a function of the number of days after implantation.

Figure 13 represents a graph illustrating the concentration of anastrozole in the implants placed subcutaneously or intraperitoneally as a function of time.

Figure 14 represents a schematic overview of a proposed metabolic pathway for celecoxib in rats. M3: HO-celecoxib; M2: HOOC-celecoxib.

Figure 15 represents a graph illustrating the concentration of HO-celecoxib in serum (panel A) or in peritoneal liquid (PL) (panel B) of rats as a function of the number of days after implantation.

Figures 16 and 17 represent graphs illustrating the concentration HOOC-celecoxib 1 and HOOC-celecoxib 2, respectively, (cis/trans isomers of HOOC-celecoxib), in serum (panels
A) or in peritoneal liquid (PL) (panels B) of rats as a function of the number of days after implantation.

**DETAILED DESCRIPTION OF THE INVENTION**

In the following passages, different aspects of the invention are described in more detail. Each aspect so described may be combined with any other aspect or aspects unless clearly indicated to the contrary. In particular, any feature indicated as being preferred or advantageous may be combined with any other feature or features indicated as being preferred or advantageous.

In the context of the present invention, the terms used are to be construed in accordance with the following definitions, unless a context dictates otherwise.

As used herein, the singular forms "a", "an", and "the" include both singular and plural referents unless the context clearly dictates otherwise.

The terms "comprising", "comprises" and "comprised of" as used herein are synonymous with "including", "includes" or "containing", "contains", and are inclusive or open-ended and do not exclude additional, non-recited members, elements or method steps.

The recitation of numerical ranges by endpoints includes all numbers and fractions subsumed within the respective ranges, as well as the recited endpoints.

The term "about" as used herein when referring to a measurable value such as a parameter, an amount, a temporal duration, and the like, is meant to encompass variations of +/-10% or less, preferably +/-5% or less, more preferably +/-1% or less, and still more preferably +/-0.1% or less of and from the specified value, insofar such variations are appropriate to perform in the disclosed invention. It is to be understood that the value to which the modifier "about" refers is itself also specifically, and preferably, disclosed.

In a first aspect, the present invention provides to an implant for delivering at least one active ingredient, said implant comprising: a core material comprising polydimethylsiloxane (PDMS) or at least one hydrogel polymer; a tube encasing said core material comprising an ethylene vinyl acetate polymer or at least one hydrogel polymer; and a sealant for closure of the open ends of said tube comprising PDMS or a mono-, di-, or triacetoxy derivative thereof, or at least one hydrogel polymer; and at least one active ingredient; with the proviso that when the sealant is said at least one hydrogel polymer, the core material comprises PDMS.
Preferably, the present invention provides an implant comprising: (a) a core material comprising polydimethylsiloxane or at least one hydrogel polymer; (b) a tube encasing said core material comprising an ethylene vinyl acetate polymer or at least one hydrogel polymer; (c) a sealant for closure of the open ends of said tube comprising polydimethylsiloxane or a mono-, di-, or triacetoxy derivative thereof, or at least one hydrogel polymer; and (d) at least one active ingredient; wherein said at least one active ingredient is selected from the group comprising celecoxib, sulindac, tamoxifen, oestrogen, oestradiol, ethinyl oestradiol, mestranol, dienogest, norgestrel, levonorgestrel, desogestrel, norgestimate, ethynodiol diacetate, leuprolelin, buserelin, gonrelin, triptorelin, nafarelin, deslorelin, histrelin, and supprelin.

In an embodiment, the present invention provides an implant comprising (a) a core material comprising polydimethylsiloxane or at least one hydrogel polymer; (b) a tube encasing said core material comprising an ethylene vinyl acetate polymer or at least one hydrogel polymer; (c) a sealant for closure of the open ends of said tube comprising polydimethylsiloxane or a mono-, di-, or triacetoxy derivative thereof, or at least one hydrogel polymer; and (d) at least one active ingredient selected from an anti-inflammatory agent; a steroid selected from estrogens or progestogens; or a gonadotropin-releasing hormone agonist; wherein said anti-inflammatory agent is selected from celecoxib and sulindac, wherein said estrogen is selected from the group comprising tamoxifen, oestrogen, oestradiol, ethinyl oestradiol, mestranol; wherein said progestogen is selected from the group comprising dienogest, norgestrel, levonorgestrel, desogestrel, norgestimate, ethynodiol diacetate, and wherein said gonadotropin-releasing hormone agonist is selected from the group comprising leuprolelin, buserelin, gonrelin, triptorelin, nafarelin, deslorelin, histrelin, and supprelin; and with the proviso that when the sealant is said at least one hydrogel polymer, the core material comprises polydimethylsiloxane.

According to an embodiment of the invention, the core material of the implants of the invention is composed of polydimethylsiloxane (PDMS). Preferably, medical grade PDMS is used. Suitable non-limiting example of medical grade PDMS which can be used as a core material is for instance PDMS with the designations MED-4211, MED-4244, MED-4286, MED-4420, MED-6210, MED-6215, MED-6219, MED-6233, MED-6385, MED-6820 and MED-6380 (Nusil technology, Carpinteria, CA, USA).

In some embodiments, the core material of the present implant comprises from about 25 % to about 60% by weight of PDMS. For example, the core material comprises from about 30% to about 60% by weight of PDMS, for example from about 35% to about 60% by weight of PDMS, for
example from about 45% to about 60% by weight of PDMS, for example from about 50% to about 60% by weight of PDMS, for example from about 55% to about 60% by weight of PDMS.

In another embodiment, the core material of the present implant comprises at least one hydrogel polymer. Various hydrogel polymers can be used, such as those obtained by homopolymerization or copolymerization of 2-hydroxyethyl methacrylate (HEMA), hydroxypropyl methacrylate (HPMA) or ethylene glycol dimethacrylate (EGDMA). In some embodiments, said hydrogel polymer comprises from about 99% to about 99.9% by weight of HEMA and from about 0.1% to about 1% by weight of EGDMA. In another embodiment, said hydrogel polymer comprises from about 95% to about 50% by weight of HEMA, from about 5% to about 50% by weight of HPMA and from about 0.1% to about 1% by weight of EGDMA. In a preferred embodiment, said hydrogel polymer comprises about 99.9% by weight of HEMA and about 0.1% by weight of EGDMA.

In some embodiments, the invention provides an implant, wherein the core material comprises from about 25% to about 60% by weight of at least one hydrogel polymer. For example, the core material comprises from about 30% to about 60% by weight of hydrogel polymer, for example from about 35% to about 60% by weight of hydrogel polymer, for example from about 40% to about 60% by weight of hydrogel polymer, for example from about 45% to about 60% by weight of hydrogel polymer, for example from about 50% to about 60% by weight of hydrogel polymer, for example from about 55% to about 60% by weight of hydrogel polymer.

In an embodiment, the tubes encasing the core material of the implants of the invention comprise an ethylene vinyl acetate (EVA) polymer. In an embodiment, the EVA polymer has a vinyl acetate content of less than 45% by weight. Preferably, the EVA polymer has a vinyl acetate content of between 5 and 40% by weight. For example, the EVA polymer has a vinyl acetate content of between 7% and 40% by weight, for example between 7% and 35% by weight, preferably between 7% and 30% by weight, preferably between 7% and 20% by weight, preferably between 7% and 10% by weight. More preferably, the EVA polymer has a vinyl acetate content of at least 5%, at least 6%, at least 7%, at least 7.5%, at least 10%, at least 15%, at least 18%, at least 20%, at least 25%, at least 28%, or at least 30% by weight. More preferably, the EVA polymer has a vinyl acetate content of 5, 6, 7, 7.5, 10, 15, 18, 20, 25, 28, or 30% by weight. In a further embodiment, the ethylene vinyl acetate polymer has a melt index of less than 10g/10 min, and preferably less than or equal to 8g/10 min. Suitable EVA polymers which can be used as a membrane are for instance Evatane® (Arkema) with the designations 501/502 (melt index 2, vinyl acetate
content 7.5%), 554/555 (4, 12.5%), 540 (10, 18%), 571 (8, 15%), 1080 VN 5 and 1040 VN 4 and Elvax® (Dupont) with the designations 450, 460, 470, 550, 560, 650, 660, 670, 750, 760, 770 and in particular 3120, 3124, 3128, 3129, 3130, 3150, 3165, 3170, 3174, 3180, 3182, 3185 and 3190.

5 In another embodiment, the tubes encasing the core material of the implants of the invention comprise at least one hydrogel polymer. Various hydrogel polymers can be used, such as those obtained by homopolymerization or copolymerization of 2-hydroxyethyl methacrylate (HEMA), hydroxypropyl methacrylate (HPMA) or ethylene glycol dimethacrylate (EGDMA). In some embodiments, said hydrogel polymer comprises from about 99% to about 99.9% by weight of HEMA and from about 0.1% to about 1% by weight of EGDMA. In another embodiment, said hydrogel polymer comprises from about 95% to about 50% by weight of HEMA, from about 5% to about 50% by weight of HPMA and from about 0.1% to about 1% by weight of EGDMA. In a preferred embodiment said hydrogel polymer comprises about 99.9% by weight of HEMA and about 0.1% by weight of EGDMA.

In some embodiments, the tubes encasing the core material of the implants and comprising an EVA polymer have a thickness ranging from about 100 μm to about 300 μm. For example, the tubes comprising an EVA polymer have a thickness ranging from about 150 μm to 300 μm, for example ranging from about 200 μm to 300 μm, for example ranging from about 250 μm to 300 μm. Preferably, the tubes comprising an EVA polymer have a thickness of about at least 100 μm, at least 110 μm, at least 120 μm, at least 130 μm, at least 140 μm, at least 150 μm, at least 160 μm, at least 170 μm, at least 180 μm, at least 190 μm, at least 200 μm, at least 210 μm, at least 220 μm, at least 230, at least 240, at least 250, at least 260, at least 270, at least 280, at least 290, or at most 300 μm. For example, the tubes comprising an EVA polymer have a thickness of about 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 210, 220, 230, 240, 250, 260, 270, 280, 290, or 300 μm, or a value in the range between any two of the aforementioned values. Preferably, the tubes comprising an EVA polymer have a thickness of about 200 μm.

In some embodiments, the tubes encasing the core material of the implants and comprising at least one hydrogel polymer have a thickness ranging from about 100 μm to about 600 μm. For example, the tubes comprising at least one hydrogel polymer have a thickness ranging from about 200 μm to about 600 μm, for example ranging from about 300 μm to about 600 μm, for example ranging from about 400 μm to about 600 μm, for example ranging from about 500 μm to about 600 μm. Preferably, the tubes comprising at least one hydrogel polymer have a thickness of about at least 100 μm, at least 150 μm, at
least 200 µm, at least 250 µm, at least 300 µm, at least 350 µm, at least 400 µm, at least 450 µm, at least 500 µm, at least 550 µm, or at most 600 µm. For example, the tubes comprising at least one hydrogel polymer have a thickness of about 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, or 600 µm, or a value in the range between any two of the aforementioned values. Preferably, the tubes comprising at least one hydrogel polymer have a thickness of about 500 µm.

According to a preferred embodiment, the sealant for closure of the open ends of the tubes comprises PDMS or a mono-, di-, or triacetoxy derivative thereof. Preferably, medical grade PDMS or a mono-, di-, or triacetoxy derivative thereof is used. For example, MED-2000 adhesive silicone of Nusil technology (Carpinteria, CA, USA) is used to seal the open ends of the implant. The sealant is chosen in order to control drug release of the implant.

According to an embodiment, the sealant for closure of the open ends of the tubes comprises at least one hydrogel polymer, with the proviso that when the sealant is said at least one hydrogel polymer, the core material comprises PDMS. Various hydrogel polymers can be used as a sealant, such as those obtained by homopolymerization or copolymerization of 2-hydroxyethyl methacrylate (HEMA), hydroxypropyl methacrylate (HPMA) or ethylene glycol dimethacrylate (EGDMA). In an embodiment, said hydrogel polymer comprises from about 99% to about 99.9% by weight of HEMA and from about 0.1% to about 1% by weight of EGDMA. In another embodiment, said hydrogel polymer comprises from about 95% to about 50% by weight of HEMA, from about 5% to about 50% by weight of HPMA and from about 0.1% to about 1% by weight of EGDMA. In a preferred embodiment said hydrogel polymer comprises about 99.9% by weight of HEMA and about 0.1% by weight of EGDMA.

The present inventors have found that implants according to the present invention allow controlled liberation of the enclosed drug. The implants according to the present invention are designed in order to allow a controlled release of at least one active ingredient over the functional useful life of the implant. This should preferably be at least 180 days and more preferably one year or longer. Implants capable of delivering at least one active ingredient evenly over 180 days and longer are particularly preferred and implants capable of delivering at least one active ingredient evenly over one year or longer are even more particularly preferred.

In an embodiment, an implant is provided wherein said core material comprises polydimethylsiloxane, wherein said tube enclosing said core material comprises an
ethylene vinyl acetate polymer, and wherein said sealant for closure of the open ends of said tube comprises polydimethylsiloxane or a mono-, di-, or triacetoxy derivative thereof.

In an embodiment, an implant is provided wherein said core material comprises polydimethylsiloxane, wherein said tube encasing said core material comprises at least one hydrogel polymer; and wherein said sealant for closure of the open ends of said tube comprises polydimethylsiloxane or a mono-, di-, or triacetoxy derivative thereof.

In an embodiment, the implants of the present invention comprise a PDMS core provided in an EVA tube and a sealant for closure of the open ends of said tube comprising PDMS or a mono-, di-, or triacetoxy derivative thereof. In another embodiment, the implants of the present invention comprise a PDMS core provided in a hydrogel polymer tube and a sealant for closure of the open ends of said tube comprising PDMS or a mono-, di-, or triacetoxy derivative thereof. In another embodiment, the implants of the present invention comprise a PDMS core provided in a hydrogel polymer tube and a sealant for closure of the open ends of said tube comprising at least one hydrogel polymer.

In an embodiment, the implants are preferably of essentially cylindrical shape with a maximal external diameter of about 4 mm. Preferably, the implants have an external diameter ranging from 2 mm to 4 mm; for examples the implant can have an external diameter of at least 2 mm, for example at least 2.5 mm, for example at least 3 mm, for example at least 3.5 mm or for example at least 4 mm.

In an embodiment, the implants are preferably of essentially cylindrical shape with a length of less than about 5 cm. Preferably, the implants have a length ranging from 1 cm to 4 cm; for example the implant have a length of at least 1 cm, for example of at least 1.5 cm, for example of at least 2 cm, for example of at least 2.5 cm, for example of at least 3 cm, for example of at least 3.5 cm; or for example of at least 4 cm.

In an embodiment, the implants are preferably of essentially cylindrical shape with a maximal external diameter of about 4 mm and a length of less than about 5 cm. Preferably, the implants are of cylindrical shape with an external diameter between 2 and 4 mm and a length between 1 and 4 cm. For example, the implants are of cylindrical shape with an external diameter of 2, 2.5, 3, 3.5 or 4 mm, or a value in the range between any two of the aforementioned values, and a length of 1, 1.5, 2, 2.5, 3, 3.5 or 4 cm, or a value in the range between any two of the aforementioned values. More preferable, the
implants are of cylindrical shape with an external diameter of about 3 mm and a length of about 2 cm. The diameter of the core material of the implant is obviously sufficient to fit within the tube encasing the core material. Of course, depending upon the circumstances, it may be necessary or desirable to increase the length or diameter of the implant or to change it from a cylindrical configuration to a different geometry. In this regard, other geometric shapes, including, for example, rings, loops, and discs, are contemplated for the present invention. However, as it is necessary to produce the implant in such a way as not to cause an impediment or to cause discomfort to the user, it is preferable to keep it as small and unobtrusive as possible.

In an embodiment, said implant comprises an inert metal coating and/or at least one radiopaque material. In an embodiment, the implant comprises said radiopaque material in the core material or in the sealant of the implant. In another embodiment, the implant comprises said radiopaque material in the core material and in the sealant of the implant.

In an embodiment, said implant comprises at least 0.01% by weight of an inert metal coating and/or at least 0.01% of at least one radiopaque material.

In an embodiment, said radiopaque material is provided in the core material. In this embodiment the core material can comprise from about 0.01% to about 60% by weight of radiopaque material, for example from about 0.1% to about 55% by weight of radiopaque material, for example from about 1% to about 50% by weight, for example from about 1% to about 40% by weight, for example from about 1% to about 30% by weight, for example from about 1% to about 20% by weight of radiopaque material. For example, the core material can comprise at least 0.01%, at least 0.1%, at least 1%, at least 5%, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55% or at most 60% by weight of radiopaque material.

For example, the core material can comprise about 0.01%, 0.1%, 1%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55% or 60% by weight of radiopaque material. In an embodiment, said radiopaque material is provided in the sealant. In this embodiment the sealant can comprise from about 0.01% to about 40% by weight of radiopaque material, for example from about 0.1% to about 35% by weight, for example from about 1% to about 30% by weight, for example from about 1% to about 25% by weight, for example from about 1% to about 20% by weight of radiopaque material. For example, the sealant material can comprise at least 0.01%, at least 0.1%, at least 1%, at least 5%, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35% or at most 40% by weight of radiopaque material. For example, the sealant material can comprise
about 0.01%, 0.1%, 1%, 5%, 10%, 15%, 20%, 25%, 30%, 35% or 40% by weight of radiopaque material.

In an embodiment, the radiopaque material may be selected from the group comprising barium, gold, platinum, tantalum, bismuth and iodine or salts thereof, or a radiopaque polymer. The radiopaque material can be incorporated into the implant in several ways. Biocompatible non-immunogenic metals such as gold and platinum may be incorporated as a very fine dispersion with particle sizes less than a few micrometers. Other heavy atoms may be incorporated in the form of inorganic salts, such as barium sulfate. In an embodiment, the radiopaque material is a radiopaque polymer. The radiopaque polymer may also be incorporated in the implant by using radiopaque (meth)acrylic monomers during the preparation of the implant (Saralidze et al., Biomacromolecules 4(3): 793-8, 2003). In an embodiment, said radiopaque (meth)acrylic monomer is 2-[2',3',5'-triiodobenzoyl]oxoethyl methacrylate. This methacrylate is intrinsically radiopaque and capable of absorbing X-radiation.

The incorporation of a radiopaque material in the implant allows localization of the implant in the body. This localization is important to follow the implant during implantation and to allow easy removal of the implant after treatment. The implants of the present invention comprising a radiopaque material can be detected using X-ray techniques. X-ray techniques are performed as known by the skilled man in the art.

In a preferred embodiment, said radiopaque material is barium sulfate. In an embodiment said barium sulfate is provided in the sealant. In this embodiment the sealant can comprise from about 0.01% to about 40% by weight of barium sulfate, for example from about 0.1% to about 35% by weight, for example from about 1% to about 30% by weight, for example from about 1% to about 25% by weight, for example from about 1% to about 20% by weight, for example from about 1% to about 15% by weight, for example from about 1% to about 10% by weight, for example from about 1% to about 5% by weight.

20 In an embodiment, the sealant can comprise at least 0.01%, at least 0.1%, at least 1%, at least 5%, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35% or at most 40% by weight of barium sulfate. For example, the sealant can comprise about 0.01%, 0.1%, 1%, 5%, 10%, 15%, 20%, 25%, 30%, 35% or 40% by weight of barium sulfate. In an embodiment, said implant comprises at least 0.01% by weight of an inert metal coating and/or at least one radiopaque material. In another embodiment, said barium sulfate is provided in the core material. In this embodiment the core material can comprise from about 0.01 to about 60% by weight of barium sulfate, for example from about 0.1% to about 55% by weight, for example from about 1% to about 50% by weight, for example from about 1% to about 40% by weight, for example from about 1% to about 30% by weight, for example from about 1% to about 25% by weight, for example from about 1% to about 20% by weight, for example from about 1% to about 15% by weight, for example from about 1% to about 10% by weight, for example from about 1% to about 5% by weight, for example from about 1% to about 35% or at most 40% by weight of barium sulfate. For example, the core material can comprise about 0.01%, 0.1%, 1%, 5%, 10%, 15%, 20%, 25%, 30%, 35% or 40% by weight of barium sulfate.
20% by weight of barium sulfate. For example, the core material can comprise at least 0.01%, at least 0.1%, at least 1%, at least 5%, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55% or at most 60% by weight of barium sulfate. For example, the core material can comprise about 0.01%, 0.1%, 1%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55% or 60% by weight of barium sulfate. In yet another embodiment, said barium sulfate is provided in the core material and in the sealant.

In another embodiment, the implant comprises an inert metal coating. The inert metal may be selected from the group comprising silver, gold, titanium, tungsten, barium, bismuth, platinum and palladium. Preferred metals are those known to be compatible with the human body, such as silver, gold, titanium and platinum. The inert metal can be coated on the implant as a fine layer. The thickness of the inert metal layer coated on the implant may be between 0.1 nm and 500 nm. Preferably, the thickness of the inert metal layer coated on the implant may be between 1 nm and 50 nm. For example, the thickness of the inert metal layer coated on the implant may be at least 1 nm, at least 5 nm, at least 10 nm, at least 15 nm, at least 20 nm, at least 25 nm, at least 30 nm, at least 35 nm, at least 40 nm, at least 45 nm, or at least 50 nm. For example, the thickness of the inert metal layer coated on the implant may be 1, 5, 10, 15, 20, 25, 30, 35, 40, 45, or 50 nm, or a value in the range between any two of the aforementioned values. The implant comprising an inert metal according to the present invention can be detected using ultrasound techniques. The addition of an inert metal coating on the implant allows localization of the implant in the body. This localization is important to follow the implant during implantation and to allow easy removal of the implant after treatment. Ultrasound techniques are performed as known by the skilled man in the art.

According to the invention, the implant comprises at least one active ingredient selected from an anti-inflammatory agent, a steroid, an aromatase inhibitor or a gonadotropin-releasing hormone agonist. Preferably, the implant comprises at least one active ingredient selected from an anti-inflammatory agent, a steroid, or a gonadotropin-releasing hormone agonist.

In an embodiment, the implant comprises from about 40% to about 75% by weight of at least one active ingredient as defined above. For example, said implant comprises from about 40% to about 70% by weight of at least one active ingredient, for example from about 40% to about 65% by weight, for example from about 40% to about 60% by weight of at least one active ingredient, for example from about 40% to about 55% by weight, for example from about 40% to about 50% by weight of at least one active ingredient. For
example, the implant comprises at least 40 %, at least 41%, at least 42%, at least 43%, at least 44%, at least 45%, at least 46%, at least 47%, at least 48%, at least 49%, at least 50%, at least 51%, at least 52%, at least 53%, at least 54%, at least 55%, at least 56%, at least 57%, at least 58%, at least 59% or at least 60% by weight of at least one active ingredient as defined above. For example, the implant comprises 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59 or 60% by weight of at least one active ingredient as defined above, or a value in the range between any two of the aforementioned values.

The term “anti-inflammatory agent” as used herein, refers to an agent that reduces inflammation.

The term “analgesic”, as used herein, refers to any member of the group of drugs used to relieve pain.

The term "steroid" as used herein, refers to an organic compound that contains a specific arrangement of four rings that are joined to each other. Some steroids are also anti-inflammatory agents such as glucocorticoids.

The term “aromatase inhibitor” as used herein, refers to a class of drugs that block the synthesis of estrogens.

The term “gonadotropin-releasing hormone agonist” as used herein, defines a synthetic peptide modeled after the hypothalamic neurohormone gonadotropin-releasing hormone (GnRH) that interacts with the gonadotropin-releasing hormone receptor to elicit its biologic response: the release of the pituitary hormones follicle-stimulating hormone and luteinizing hormone.

In an embodiment, said implant comprises at least one anti-inflammatory agent selected from the group comprising glucocorticoids, non-steroidal anti-inflammatory drugs and immune-selective anti-inflammatory drugs. In an embodiment, said implant comprises at least one glucocorticoid selected from the group comprising hydrocortisone (cortisol), cortisone acetate, prednisone, prednisolone, methylprednisolone, dexamethasone, betamethasone, triamcinolone, beclometasone, fludrocortisone acetate, deoxycorticosterone acetate (DOCA) and aldosterone. In an embodiment, said implant comprises at least one non-steroidal anti-inflammatory drug selected from the group consisting of propionic acid derivatives such as ibuprofen, naproxen, fenoprofen, ketoprofen, flurbiprofen, oxaprozin; acetic acid derivatives such as indomethacin, sulindac, etodolac, ketorolac, diclofenac, nabumetone, enolic acid or oxicam derivatives such as piroxicam, meloxicam, tenoxicam, droxicam, lornoxicam, isoxicam; fenamic acid
derivatives such as mafenamic acid, meclofenamic acid, flufenamic acid, tolfenamic acid; and selective COX-2 inhibitors or coxibs such as celecoxib, rofecoxib, valdecoxib, parecoxib, lumiracoxib, etoricoxib and firocoxib. In a preferred embodiment, the implant comprises at least one non-steroidal anti-inflammatory drug selected from celecoxib or sulindac.

Preferably, said implant comprises at least one anti-inflammatory drug selected from celecoxib or sulindac.

In an embodiment, the implant comprises at least one steroid selected from the group comprising estrogens, progestogens, glucocorticoids, androgens and mineralocorticoids; analogs, agonists and antagonists thereof.

In an embodiment, the implant comprises at least one estrogen selected from the group comprising tamoxifen, oestrogen, oestradiol, ethinyl oestradiol, and mestranol.

In an embodiment, the implant comprises at least one progestogen selected from the group comprising progesterone, dienogest, medroxyprogesterone acetate, norgestrel, levonorgestrel, norethindrone, norethindrone acetate, desogestrel, norgestimate, and ethynodiol diacetate. Preferably, said progestogen is dienogest.

In an embodiment, the implant comprises at least one aromatase inhibitor selected from the group comprising atamestane, exemestane, formestane, fadrozole, letrozole, pentrozole, anastrozole, and vorozole.

In an embodiment, the implant comprises at least one gonadotropin-releasing hormone agonist selected from the group comprising leuprolrelin, buserelin, gonrelin, triptorelin, nafarelin, deslorelin, histrelin, and supprelin.

As mentioned herein, the implant can comprise at least one active ingredient selected from an anti-inflammatory agent, a steroid, an aromatase inhibitor or a gonadotropin-releasing hormone agonist.

In an embodiment, the present invention provides an implant comprising: a core material comprising polydimethylsiloxane or at least one hydrogel polymer; a tube encasing said core material comprising an ethylene vinyl acetate polymer or at least one hydrogel polymer; a sealant for closure of the open ends of said tube comprising polydimethylsiloxane or a mono-, di-, or triacetoxy derivative thereof, or at least one hydrogel polymer; and at least one active ingredient; wherein said at least one active ingredient is selected from an anti-inflammatory agent, a steroid, an aromatase inhibitor or a gonadotropin-releasing hormone agonist, wherein said anti-inflammatory agent is
selected from celecoxib or sulindac, wherein said steroid is selected from the group comprising tamoxifen, oestrogen, oestradiol, ethinyl oestradiol, mestranol, dienogest, norgestrel, levonorgestrel, desogestrel, norgestimate, and ethynodiol diacetate, wherein said aromatase inhibitor selected from the group comprising atamestanse, exemestane, formestane, fadrozole, letrozole, pentrozole, anastrozole, and vorozole, wherein said gonadotropin-releasing hormone agonist is selected from the group comprising leuprolelin, buserelin, gonrelin, triptorelin, nafarelin, deslorelin, histrelin, and supprelin; and with the proviso that when the sealant is said at least one hydrogel polymer, the core material comprises polydimethylsiloxane.

Preferably, the implant comprises at least one active ingredient selected from an anti-inflammatory agent, a steroid, or a gonadotropin-releasing hormone agonist.

In an embodiment, the present invention provides an implant comprising: a core material comprising polydimethylsiloxane or at least one hydrogel polymer; a tube encasing said core material comprising an ethylene vinyl acetate polymer or at least one hydrogel polymer; a sealant for closure of the open ends of said tube comprising polydimethylsiloxane or a mono-, di-, or triacetoxy derivative thereof, or at least one hydrogel polymer; and at least one active ingredient; wherein said at least one active ingredient is selected from an anti-inflammatory agent, a steroid, or a gonadotropin-releasing hormone agonist, wherein said anti-inflammatory agent is selected from celecoxib or sulindac, wherein said steroid is selected from the group comprising estrogens and progestogens, wherein said estrogen is selected from the group comprising tamoxifen, oestrogen, oestradiol, ethinyl oestradiol, and mestranol, wherein said progestogen is selected from the group comprising dienogest, norgestrel, levonorgestrel, desogestrel, norgestimate, ethynodiol diacetate, wherein said gonadotropin-releasing hormone agonist is selected from the group comprising leuprolelin, buserelin, gonrelin, triptorelin, nafarelin, deslorelin, histrelin, and supprelin; and with the proviso that when the sealant is said at least one hydrogel polymer, the core material comprises polydimethylsiloxane.

In a preferred embodiment, the present invention provides an implant comprising: a core material comprising polydimethylsiloxane; a tube encasing said core material comprising an ethylene vinyl acetate polymer; a sealant for closure of the open ends of said tube comprising polydimethylsiloxane or a mono-, di-, or triacetoxy derivative thereof; and at least one active ingredient; wherein said at least one active ingredient is selected from an anti-inflammatory agent, a steroid, or a gonadotropin-releasing hormone agonist, wherein said anti-inflammatory agent is selected from celecoxib or sulindac, wherein said steroid is
selected from the group comprising estrogens and progestogens, wherein said estrogen is
selected from the group comprising tamoxifen, oestrogen, oestradiol, ethinyl oestradiol,
and mestranol, wherein said progestogen is selected from the group comprising
dienogest, norgestrel, levonorgestrel, desogestrel, norgestimate, ethynodiol diacetate,
wherein said gonadotropin-releasing hormone agonist is selected from the group
comprising leuprolerin, buserelin, gonrelin, triptorelin, nafarelin, deslorelin, histrelin, and
supprelin; and with the proviso that when the sealant is said at least one hydrogel
polymer, the core material comprises polydimethylsiloxane.

In a further embodiment, the present invention provides an implant comprising: a core
material comprising polydimethylsiloxane or at least one hydrogel polymer; a tube
encasing said core material comprising an ethylene vinyl acetate polymer or at least one
hydrogel polymer; a sealant for closure of the open ends of said tube comprising
polydimethylsiloxane or a mono-, di-, or triacetoxy derivative thereof, or at least one
hydrogel polymer; and at least one active ingredient; wherein said at least one active
ingredient is selected from an anti-inflammatory agent, a steroid, or a gonadotropin-
releasing hormone agonist, wherein said anti-inflammatory agent is selected from
celecoxib or sulindac, wherein said steroid is selected from the group comprising
tamoxifen, oestrogen, oestradiol, ethinyl oestradiol, mestranol, dienogest, norgestrel,
levonorgestrel, desogestrel, norgestimate, and ethynodiol diacetate, wherein said
gonadotropin-releasing hormone agonist is selected from the group comprising
leuprolerin, buserelin, gonrelin, triptorelin, nafarelin, deslorelin, histrelin, and supprelin;
and with the proviso that when the sealant is said at least one hydrogel polymer, the core
material comprises polydimethylsiloxane.

In a further embodiment, the present invention provides an implant comprising: a core
material comprising polydimethylsiloxane or at least one hydrogel polymer; a tube
encasing said core material comprising an ethylene vinyl acetate polymer or at least one
hydrogel polymer; a sealant for closure of the open ends of said tube comprising
polydimethylsiloxane or a mono-, di-, or triacetoxy derivative thereof, or at least one
hydrogel polymer; and at least one active ingredient; wherein said at least one active
ingredient is selected from the group comprising celecoxib, sulindac, tamoxifen,
oestrogen, oestradiol, ethinyl oestradiol, mestranol, dienogest, norgestrel, levonorgestrel,
desogestrel, norgestimate, ethynodiol diacetate, leuprolerin, buserelin, gonrelin, triptorelin,
nafarelin, deslorelin, histrelin, and supprelin; and with the proviso that when the sealant is
said at least one hydrogel polymer, the core material comprises polydimethylsiloxane.
In certain further embodiments, the present invention provides an implant comprising: a core material comprising polydimethylsiloxane or at least one hydrogel polymer; a tube encasing said core material comprising an ethylene vinyl acetate polymer or at least one hydrogel polymer; a sealant for closure of the open ends of said tube comprising polydimethylsiloxane or a mono-, di-, or triacetoxy derivative thereof, or at least one hydrogel polymer; and at least one active ingredient; wherein said at least one active ingredient is selected from an anti-inflammatory agent, a steroid, or a gonadotropin-releasing hormone agonist, wherein said anti-inflammatory agent is selected from celecoxib or sulindac, wherein said steroid is selected from the group comprising tamoxifen, oestrogen, oestradiol, ethinyl oestradiol, mestranol and dienogest, wherein said gonadotropin-releasing hormone agonist is selected from the group comprising leuprorelin, buserelin, gonirelin, triptorelin, nafarelin, deslorelin, histrelin, and supprelin; and with the proviso that when the sealant is said at least one hydrogel polymer, the core material comprises polydimethylsiloxane.

In certain preferred embodiments, the present invention provides an implant comprising: a core material comprising polydimethylsiloxane or at least one hydrogel polymer; a tube encasing said core material comprising an ethylene vinyl acetate polymer or at least one hydrogel polymer; a sealant for closure of the open ends of said tube comprising polydimethylsiloxane or a mono-, di-, or triacetoxy derivative thereof, or at least one hydrogel polymer; and at least one active ingredient; wherein said at least one active ingredient is selected from the group comprising celecoxib, sulindac and dienogest; and with the proviso that when the sealant is said at least one hydrogel polymer, the core material comprises polydimethylsiloxane.

In a preferred embodiment, said at least one active ingredient may be selected from the group comprising anastrozole, letrozole, exemestane, dienogest, sulindac and celecoxib.

In a more preferred embodiment, said at least one active ingredient may be selected from the group comprising anastrozole, letrozole, exemestane, dienogest, sulindac and celecoxib, and said implant also comprises barium sulfate.

In an embodiment, the present invention provides an implant comprising: a core material comprising polydimethylsiloxane or at least one hydrogel polymer; a tube encasing said core material comprising an ethylene vinyl acetate polymer or at least one hydrogel polymer; a sealant for closure of the open ends of said tube comprising polydimethylsiloxane or a mono-, di-, or triacetoxy derivative thereof, or at least one hydrogel polymer; and at least one active ingredient; wherein said at least one active
ingredient is selected from the group comprising anastrozole, letrozole, exemestane, dienogest, sulindac and celecoxib.

In a preferred embodiment, said implant comprises a PDMS core provided in an EVA tube and a sealant for closure of the open ends of said tube comprising PDMS or a mono-, di-, or triacetoxy derivative thereof, plus at least one active ingredient selected from the group comprising anastrozole, letrozole, exemestane, dienogest, sulindac and celecoxib, and also comprises barium sulfate. In another preferred embodiment, said implant comprises a PDMS core provided in a hydrogel polymer tube and a sealant for closure of the open ends of said tube comprising PDMS or a mono-, di-, or triacetoxy derivative thereof, plus at least one active ingredient selected from the group comprising anastrozole, letrozole, exemestane, dienogest, sulindac and celecoxib, and also comprises barium sulfate. In a further preferred embodiment, said implant comprises a hydrogel polymer core provided in a hydrogel polymer tube and a sealant for closure of the open ends of said tube comprising PDMS or a mono-, di-, or triacetoxy derivative thereof, plus at least one active ingredient selected from the group comprising anastrozole, letrozole, exemestane, dienogest, sulindac and celecoxib, and also comprises barium sulfate. In yet a further preferred embodiment, said implant comprises a PDMS core provided in a hydrogel polymer tube and a sealant for closure of the open ends of said tube comprising a hydrogel polymer, plus at least one active ingredient selected from the group comprising anastrozole, letrozole, exemestane, dienogest, sulindac and celecoxib, and also comprises barium sulfate.

In another aspect, the present invention relates to a method for preparing an implant comprising the steps of:

- preparing a core material comprising PDMS or at least one hydrogel polymer, and at least one active ingredient;
- injecting said core material in a tube comprising an ethylene vinyl acetate polymer or at least one hydrogel polymer;
- curing said core material in said tube;
- closing the open ends of said tube with a sealant comprising PDMS or a mono-, di-, or triacetoxy derivative thereof, or at least one hydrogel polymer, with the proviso that when the sealant is said at least one hydrogel polymer, the core material comprises PDMS.

In a further embodiment, the method for preparing an implant comprises the steps of:
- preparing a mixture of a core material comprising PDMS or at least one monomer precursor of hydrogel; an initiator; a catalyst; a cross-linker and at least one active ingredient;

- injecting said mixture in a tube comprising an ethylene vinyl acetate polymer or at least one hydrogel polymer;

- curing said mixture in said tube;

- closing the open ends of said tube with a sealant comprising PDMS or a mono-, di-, or triacetoxy derivative thereof, or at least one hydrogel polymer, with the proviso that when the sealant is said at least one hydrogel polymer, the core material comprises PDMS.

The term "curing", as used herein, defines the process of hardening a polymer. The catalyst, as used herein, may be selected from the group comprising tin octoate (SnOct₂), platinum-based catalysts and peroxides. In a preferred embodiment, the catalyst is tin octoate (SnOct₂).

In an embodiment, the cross-linker as used herein is an orthosilicate. In a preferred embodiment, the cross-linker is tetrapropyl orthosilicate (SiOP₄).

Generally, a method for preparing an implant starts with preparing a mixture of a core material comprising PDMS, or a (meth)acrylic monomer; a catalyst; a cross-linker and at least one active ingredient selected from an anti-inflammatory agent, a steroid, an aromatase inhibitor or a gonadotropin-releasing hormone agonist. This mixture is then injected into a tube comprising an ethylene vinyl acetate polymer or a hydrogel polymer. After curing of the mixture in the tube, the open ends of the tube are closed with a sealant comprising PDMS or a mono-, di-, or triacetoxy derivative thereof.

In an embodiment, the present invention relates to a method for preparing an implant comprising a PDMS core provided in an EVA tube and a sealant for closure of the open ends of said tube comprising PDMS or a mono-, di-, or triacetoxy derivative thereof. These implants can be synthesized by curing of PDMS in the EVA tube. The method for preparing implants comprising PDMS core in EVA tubes closed with a sealant can start with transferring PDMS and at least one active ingredient into a container. The mixture comprising PDMS and active ingredient can then be placed at temperature below 0°C, for about 5 min to several hours, for example at -20°C for about 1 hour. Then, cross-linker and catalyst can be mixed together in a separate container. The mixture of the catalyst and the cross-linker can then be added into the cold mixture comprising PDMS and active ingredient. The PDMS-active ingredient-cross-linker-catalyst mixture (PDMS mixture) can
be homogenized before being preferably placed under vacuum in order to remove the air
trapped in the blend. The PDMS mixture can be finally transferred into a dispensing
device such as a syringe and kept at temperature below 0°C, for example at -20°C. EVA
tubes can be prepared by extrusion of EVA pellets into molds. The PDMS mixture can
then be injected into an EVA tube. In an embodiment, the ends of the tube can be closed
with a parafilm. After about 12h to 24h of curing at room temperature for example, the
tubes can be cut in order to obtain implants of suitable size. The implant extremities can
then be closed with PDMS or a mono-, di-, or triacetoxy derivative thereof (also referred
herein as adhesive silicone). In an embodiment, the implants can then be subjected to
vacuum and/or heat to remove the propanol formed during the PDMS cross-linking.

In a further embodiment, the present invention provides a method for preparing an implant
comprising a PDMS core provided in a hydrogel of poly(HEMA) tube and a sealant for
closure of the open ends of said tube comprising PDMS or a mono-, di-, or triacetoxy
derivative thereof. The method for preparing implants comprising a PDMS core in
hydrogel polymer tubes closed with a sealant can start with transferring PDMS and at
least one active ingredient into a container. The mixture comprising PDMS and active
ingredient can then be placed at temperature below 0°C, for 5 min to several hours, for
example mixture can be placed at -20°C for 1 hour. Then, cross-linker and catalyst can be
mixed together in a separate container. The mixture of the catalyst and the cross-linker
can then be added into the cold PDMS-active ingredient mixture. The PDMS-active
ingredient-cross-linker-catalyst mixture (PDMS mixture) can be homogenized before being
preferably placed under vacuum in order to remove the air trapped in the blend. The
PDMS mixture can be finally transferred into a dispensing device such as a syringe and if
necessary kept at temperature below 0°C, for example at -20°C. The tubes of poly(HEMA)
can be synthesized by the polymerization of hydroxyethyl methacrylate (HEMA) in a
hollow cylinder mold. After repeated wash steps to remove unreacted HEMA, the tubes
can be completely dehydrated. This dehydration step can help in completely hardening
the tubes and make them resistant to the injection of the PDMS, and also avoids
deactivation of the cross-linker, which is sensitive to water. The PDMS can then be
injected into the hydrogel tubes. After about 12h to 24h of curing at room temperature for
example, the tubes can be cut in order to obtain implants of suitable size. The implant
extremities can then be closed with PDMS or a mono-, di-, or triacetoxy derivative thereof.
In an embodiment, the implants can then be subjected to vacuum and/or heat to remove
the propanol formed during the PDMS cross-linking.
In an embodiment, the present invention relates to a method for preparing an implant comprising at least one hydrogel polymer core provided in a hydrogel polymer tube and a sealant for closure of the open ends of said tube comprising PDMS or a mono-, di-, or triacetoxy derivative thereof. The method for preparing implants comprising a core in a hydrogel polymer closed with a sealant can start with transferring to recipient freshly distilled hydroxyethyl methacrylate (HEMA) and at least one active ingredient. In an embodiment, said HEMA can contain 0.1% in weight of ethylene glycol dimethacrylate (EGDMA). The solution can be degassed using an inert gas (such as nitrogen bubbling) and subsequently, ammonium persulfate (APS) aqueous solution and tetramethylethylenediamine (TEMED) can be added. After short homogenization, the solution can be transferred to hollow tubing wherein polymerization occurs. The implants can then be collected. The ends of the implants can then be cut and the implant extremities can then be closed with adhesive silicone. The polyHEMA implants can then be washed by repeated immersion in sterile water to remove unreacted HEMA.

In another embodiment, the method for preparing hydrogel polymer implants closed with a sealant can start with transferring to recipient freshly distilled hydroxyethyl methacrylate (HEMA) and at least one active ingredient into a container. In an embodiment, said HEMA can contain 0.1% in weight of ethylene glycol dimethacrylate (EGDMA). The solution can be degassed using an inert gas (such as nitrogen bubbling) and subsequently, a mixture of potassium persulfate and potassium bisulfite can be added. After short homogenization, the solution can be transferred to hollow tubing wherein polymerization occurs. The implants can then be collected. The ends of the implants can then be cut and the implant extremities can then be closed with adhesive silicone. The polyHEMA implants can then be washed by repeated immersion in sterile water to remove unreacted HEMA.

In a further embodiment, the present invention provides a method for preparing an implant comprising a PDMS core provided in a hydrogel of poly(HEMA) tube and a sealant for closure of the open ends of said tube comprising a hydrogel polymer. The method for preparing implants comprising PDMS core in hydrogel polymer tubes closed with a hydrogel polymer sealant can start with transferring PDMS and at least one active ingredient into a container. The mixture comprising PDMS and active ingredient can be placed at temperature below 0°C, for 5 min to several hours, for example PDMS can be place at -20°C for 1 hour. Then, cross-linker and catalyst can be mixed together in a separate container. The mixture of the catalyst and the cross-linker can then be added into the cold PDMS mixture. The PDMS-cross-linker-catalyst mixture can be homogenized before being preferably placed under vacuum in order to remove the air trapped in the
blend. The PDMS mixture can be finally transferred into a dispensing device such as a syringe and if necessary kept at temperature below 0°C, for example at -20°C. The tubes of poly(HEMA) can be synthesized by the polymerization of hydroxyethyl methacrylate (HEMA) in a hollow cylinder mold. After repeated wash steps to remove unreacted HEMA, the tubes can be completely dehydrated. This dehydration step can help in completely hardening the tubes and make them resistant to the injection of the PDMS, and also avoids deactivation of the cross-linker, which is sensitive to water. The PDMS can then be injected into the hydrogel tubes. After about 12h to 24h of curing at room temperature for example, the tubes can be cut in order to obtain implants of suitable size. The implant extremities can then be closed with a hydrogel polymer sealant. The sealant is prepared by transferring to a recipient freshly distilled hydroxyethyl methacrylate (HEMA) and subsequently, adding a mixture of potassium persulfate and potassium bisulfite. After short homogenization, the solution can be transferred to a dispensing device wherein polymerization is allowed to start to increase the viscosity of the solution. The hydrogel sealant can then be used to close the implant extremities. In an embodiment, the implants can then be subjected to vacuum and/or heat to remove the propanol formed during the PDMS cross-linking.

The present invention further relates to a method for preparing an implant as described above comprising the additional step of adding a radiopaque material and/or inert metal coating to the implant. In a particular embodiment, the invention relates to a method for preparing an implant comprising the step of adding at least 0.01% by weight of a radiopaque material to the implant. The invention present invention also encompasses a method for preparing an implant comprising the step of adding at least 0.01% by weight of a radiopaque material to the core material and/or to the sealant of the implant. The present invention also encompasses a method for preparing an implant comprising the step of coating an implant with at least 0.01% by weight of an inert metal coating.

In a second aspect, the invention provides an implant for use as a medicament. Particularly, the invention provides an implant for use in the treatment of endometriosis.

The present invention provides an implant for use as a medicament, wherein said implant can be administered intraperitoneally or subcutaneously. In a particular embodiment, the present invention provides an implant for use in the treatment of endometriosis, wherein said implant can be administered intraperitoneally or subcutaneously. The subcutaneous administration of the implant is in such a way to ensure the sustained delivery of a therapeutically effective amount of the at least one enclosed active ingredient. The intraperitoneal administration of the implant is in such a way to ensure the localized and
sustained delivery of a therapeutically effective amount of the at least one enclosed active ingredient. The term "therapeutically effective amount" as used herein refers to an amount of active ingredient or pharmaceutical agent that elicits the biological or medicinal response in a tissue, system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes alleviation of the symptoms of the disease being treated.

In an embodiment, the present invention relates to a method for the treatment of endometriosis comprising the step of administering at least one implant according to the invention to an individual in need thereof. In another aspect, the present invention provides a method for the treatment of endometriosis, comprising the step of administering intraperitoneally or subcutaneously at least one implant according to the invention to an individual in need thereof. The term "individual" as used herein refers to a mammal. The individual will preferably be a human.

In a further embodiment, the present invention relates to a method for the treatment of endometriosis, wherein said at least one implant according to the present invention is administered once per 180 days, or less frequently, preferably once per year, or less frequently. The implants of the present invention may be administered at any suitable time interval, preferably once per six months, once yearly, once every 18 months or at any time interval in between, or even less frequently, e.g. every 2-5 years, or even for once only dosing. Typically, the implant is for administration once every 6 months or less frequently. Yet more preferably the composition is for once yearly administration or less frequently. Alternatively, the composition is for once only dosing. The implant may on the other hand be readministered at a later time, in the event of a relapse as defined by symptoms and/or clinical assay.

In an embodiment, the present invention relates to an implantable system comprising: at least one first implant according to the present invention, wherein said at least one first implant comprises at least one active ingredient selected from an anti-inflammatory agent, a steroid, an aromatase inhibitor or a gonadotropin-releasing hormone agonist; and at least one second implant comprising at least one active ingredient selected from an anti-inflammatory agent, a steroid, an aromatase inhibitor or a gonadotropin-releasing hormone agonist. In another embodiment, the present invention relates to an implantable system, as described above, wherein said second implant is also an implant according to the present invention.

In a particular embodiment, the invention provides an implantable system comprising: at least one first implant comprising at least one active ingredient used as an analgesic,
selected from an anti-inflammatory agent; and at least one second implant comprising at least one active ingredient able to influence hormone activity, selected from an anti-inflammatory agent, a steroid, an aromatase inhibitor or a gonadotropin-releasing hormone agonist. In an embodiment, the implantable system according to the present invention is designed to include sufficient active agent so as to provide the individual with a required daily dose of a therapeutically effective amount of the active ingredient over the functional useful life of the implants. In a further embodiment, the rate at which the at least one active ingredient is provided from the implantable system to the individual is relatively constant and in such a way to ensure the sustained delivery of a therapeutically effective amount of the at least one enclosed active ingredient.

The present invention also relates to an implantable system, wherein said at least one first implant and said at least one second implant are of a cooperative size and shape and are designed such that each releases a pharmaceutically complementary amount of at least one active ingredient, so as to provide treatment to an individual diagnosed with endometriosis.

The invention will now be illustrated by means of the following synthetic and biological examples, which do not limit the scope of the invention in any way.

**EXAMPLES**

**Example 1: Production of polydimethylsiloxane implants**

Typically, 19.4 g of polydimethylsiloxane (PDMS, base, medical grade) was placed in a sterile container and kept at -20°C for 1 hour. Thereafter, 0.5 g of tetrapropyl orthosilicate (SiOP₄, cross-linker, medical grade) and 0.1 g of tin octoate (SnOct₂, catalyst, medical grade) were mixed together in a separate glass container. This mixture of catalyst and cross-linker was then added to the cold PDMS under a laminar flow hood. The PDMS blend was manually mixed for 2 minutes before being placed under a vacuum for 5 minutes in order to remove trapped air bubbles. The PDMS mixture was finally transferred to a plastic syringe and maintained at -20°C.

PDMS implants were prepared by cross-linking the PDMS mixture in a mold at 80°C. This mold, composed of an iron core covered with Teflon film, allows preparation of 12 implants of 20 mm in length and 3 mm in diameter in a row. The PDMS mixture contained in the syringe was injected into the mold, which was then compressed at 80°C under a pressure of 30 bars. After 15 minutes, the mold was cooled at room temperature and the collected implants were transferred to a sterile device. The implants were then placed in a
Vismara vacuum oven (VO65) at 950 mbar for 4 hours at room temperature to remove the propanol resulting from the PDMS cross-linking.

**Example 2: Production of ethylene vinyl acetate implants**

Ethylene vinyl acetate (EVA) implants were prepared by extrusion of EVA pellets (Elvax 53129, Dupont) in a micro-extruder (DSM 5 cm³ micro-extruder equipped with a twin-screw). For this purpose, EVA pellets were immersed in ethanol in order to extract butyl hydroxytoluene (BHT). After filtration, they were dried under a vacuum at room temperature. Thereafter, 8 g of EVA was introduced into the twin-screw micro-extruder at 80°C at a rotation rate of 100 rpm. After 5 minutes of mixing, the resulting EVA rods were collected and directly placed into sterile water, primarily to fix their geometry, but also to avoid adsorption of dirt onto the surface. The rods were then cut into 2 cm implants and stored in a sterile bag.

**Example 3: Production of poly(hydroxyethyl methacrylate) implants**

Typically, 5 ml of freshly distilled hydroxyethyl methacrylate (HEMA) containing 0.1% in weight of ethylene glycol dimethacrylate (EGDMA) was transferred to a glass tube. After degassing the solution by nitrogen bubbling for 5 minutes, 1.67 ml of ammonium persulfate (APS) aqueous solution (APS concentration = 0.024 mol/l) and 7 μl of tetramethylthelylenediamine (TEMED) were added. After short homogenization, the solution was transferred to an insulin syringe used as a sterile and disposable mold. The syringes were placed under a laminar flow hood at room temperature for 12 hours to allow polymerization. The implants were then collected by applying simple pressure to the syringe piston. The ends of the implants were cut to obtain implants of 2 cm long (diameter 3 mm). The poly(HEMA) implants were then washed by repeated immersion in sterile water to remove unreacted HEMA. After washing 5 times, the implants were placed in a sterile aqueous solution.

**Example 4: Biocompatibility test of PDMS, EVA and poly(HEMA) implants**

Implants were prepared as in example 1, 2 and 3 and the biocompatibility of the 3 polymers, PDMS, EVA and poly(HEMA), was tested in the peritoneal cavity of rats, rabbits and rhesus monkeys. Implants of 20 mm in length and 3 mm in diameter were placed in the peritoneal cavity of 30 rabbits, 30 rats and 3 rhesus monkeys. Inflammation was evaluated by regular hematological analyses and measurement of inflammatory markers such as C-reactive protein and fibrinogen throughout the experiment and by post-mortem examination of the peritoneal cavity. After 3 or 6 months, the animals were euthanized.
The implants were macroscopically examined for signs of encapsulation and removed for histological analysis.

Hematological analyses, measurement of inflammatory markers and peritoneal macroscopic examination showed no evidence of inflammation. Histological analysis revealed fibrous tissue encapsulating PDMS and EVA implants in all 3 species and poly(HEMA) implants in rabbits and monkeys. In rats, poly(HEMA) implant surfaces remained relatively free. Calcium deposits were observed inside poly(HEMA) implants in rats and monkeys, but not in rabbits. The results demonstrate that PDMS, EVA and poly(HEMA) polymers are biocompatible in the peritoneal cavity of rats, rabbits and rhesus monkeys.

Example 5: Synthesis of implants comprising anastrozole as active ingredient according to an embodiment of the invention

The implants comprising a PDMS core were synthesized by curing of PDMS in an ethylene vinyl acetate (EVA) tube. Typically, 19.4 g of PDMS (base, medical grade) and 19.5 g of freshly ground anastrozole (APIN Chemicals Limited, Abingdon, United Kingdom) was transferred into a sterile container before homogenizing the mixture with an ultraturrax T 25 basic (Ika, Staufen, Germany). The blend was placed at -20°C for 1 hour. Then, 0.5 g of tetrapropyl orthosilicate (SiOP₄₉, cross-linker, medical grade) and 0.1 g of tin octoate (SnOct₂, catalyst, medical grade) were mixed together in a separate glass container. The mixture of the catalyst and the cross-linker was then added into the cold PDMS mixture inside a laminar flow hood. The PDMS-anastrozole-cross-linker-catalyst mixture was manually homogenized for 2 minutes before being placed under vacuum during 5 minutes in order to remove the air bubbles trapped in the blend. The PDMS mixture was finally transferred into a plastic syringe and kept at -20°C for at least 1 hour.

Typically, EVA tubes were prepared by extrusion of EVA pellets (Elvax 3129, Dupont) in combination with blow molding. The PDMS mixture was then injected into an EVA tube comprising 10% by weight of vinyl acetate (internal diameter of 3 mm, thickness of the wall 200 µm and 15 cm long) in a laminar flow hood. The ends of the tube were closed with a parafilm. After one night of curing at room temperature, the tubes were cut in order to obtain implants of 2 cm long. The implant extremities were closed with MED-2000 adhesive silicone (Nusil technology, Carpinteria, CA, USA). The implants were then moved in a Vismara 65 vacuum oven at 950 mbar for 4 hours at room temperature with the purpose to remove the propanol formed during the PDMS cross-linking.
Example 6: Synthesis of implants comprising celecoxib as active ingredient according to an embodiment of the invention

The implants comprising a PDMS core were synthesized by curing of PDMS in an ethylene vinyl acetate (EVA) tube. Typically, 19.4 g of PDMS (base, medical grade) and 19.5 g of celecoxib (Kemprotec Limited, Middlesbrough, United Kingdom) was transferred into a sterile container before homogenizing the mixture manually with a stainless spatula. The blend was placed at -20°C for 1 hour. Then, 0.5 g of tetrapropyl orthosilicate (SiOP$_4$, cross-linker, medical grade) and 0.1 g of tin octoate (SnOct$_2$, catalyst, medical grade) were mixed together in a separate glass container. The mixture of the catalyst and the cross-linker was then added into the cold PDMS mixture inside a laminar flow hood. The PDMS-celecoxib-cross-linker-catalyst mixture was manually homogenized for 2 minutes before being placed under vacuum during 5 minutes in order to remove the air bubbles trapped in the blend. The PDMS mixture was finally transferred into a plastic syringe and kept at -20°C for at least 1 hour.

Typically, ethylene vinyl acetate (EVA) tubes were prepared by extrusion of EVA pellets (Elvax 3182, DuPont) in combination with blow molding. The PDMS mixture was then injected into an EVA tube comprising 28 % by weight of vinyl acetate (internal diameter of 3 mm, thickness of the wall 200 μm and 15 cm long) in a laminar flow hood. The ends of the tube were closed with a parafilm. After one night of curing at room temperature, the tubes were cut in order to obtain implants of 2 cm long. The implant extremities were closed with MED-2000 adhesive silicone (Nusil technology, Carpinteria, CA, USA). The implants were then moved in a Vismara 65 vacuum oven at 950 mbar for 4 hours at room temperature with the purpose to remove the propanol formed during the PDMS cross-linking.

Example 7: Synthesis of implants comprising dienogest as active ingredient according to an embodiment of the invention

Typically, 19.4 g of PDMS (base, medical grade) and 19.5 g of dienogest was transferred into a sterile container before homogenizing the mixture manually with a stainless spatula. The blend was placed at -20°C for 1 hour. Then, 0.5 g of tetrapropyl orthosilicate (SiOP$_4$, cross-linker, medical grade) and 0.1 g of tin octoate (SnOct$_2$, catalyst, medical grade) were mixed together in a separate glass container. The mixture of the catalyst and the cross-linker was then added into the cold PDMS mixture inside a laminar flow hood. The PDMS-dienogest-cross-linker-catalyst mixture was manually homogenized for 2 minutes before being placed under vacuum during 5 minutes in order to remove the air bubbles
trapped in the blend. The PDMS mixture was finally transferred into a plastic syringe and kept at -20°C for at least 1 hour.

The PDMS-dienogest mixture was then injected into EVA tubes comprising 10, 18 or 28% by weight of vinyl acetate. The ends of the tube were closed with a parafilm. After one night of curing at room temperature, the tubes were cut in order to obtain implants of 2 cm long. The implant extremities were closed with MED-2000 adhesive silicone (Nusil technology, Carpinteria, CA, USA). The implants were then moved in a Vismara 65 vacuum oven at 950 mbar for 4 hours at room temperature with the purpose to remove the propanol formed during the PDMS cross-linking.

Example 8: Synthesis of implants comprising sulindac as active ingredient according to an embodiment of the invention

Typically, 19.4 g of PDMS (base, medical grade) and 19.5 g of sulindac (Aldrich) was transferred into a sterile container before homogenizing the mixture manually with a stainless spatula. The blend was placed at -20°C for 1 hour. Then, 0.5 g of tetrapropyl orthosilicate (SiOP4, cross-linker, medical grade) and 0.1 g of tin octoate (SnOct2, catalyst, medical grade) were mixed together in a separate glass container. The mixture of the catalyst and the cross-linker was then added into the cold PDMS mixture inside a laminar flow hood. The PDMS-sulindac-cross-linker-catalyst mixture was manually homogenized for 2 minutes before being placed under vacuum during 5 minutes in order to remove the air bubbles trapped in the blend. The PDMS mixture was finally transferred into a plastic syringe and kept at -20°C for at least 1 hour.

Typically, hydrogel tubes of poly(HEMA) were synthesized by the polymerization of hydroxyethyl methacrylate (HEMA) in a hollow cylinder mold. Typically, 5 ml of freshly distilled hydroxyethyl methacrylate (HEMA) containing 0.1% in weight of ethylene glycol dimethacrylate (EGDMA) was transferred to a glass tube. After degassing the solution by nitrogen bubbling for 5 minutes, 1.67 ml of ammonium persulfate (APS) aqueous solution (APS concentration = 0.024 mol/l) and 7 µl of tetramethyleneethylenediamine (TEMED) were added. After short homogenization, the solution was transferred into a glass tube (diameter 5 mm). A glass rod (diameter 3 mm) was then placed at the middle of the glass cylinder. After complete polymerization, the poly(HEMA) tube was removed out of the mold. After repeated wash steps to remove the unreacted HEMA, the tubes were completely dehydrated in order to completely harden the tubes and make them resistant to the injection of the PDMS-sulindac mixture, but also to avoid deactivation of the cross-linker, which is sensitive to water. The PDMS-sulindac mixture was then injected into the
hydrogel tubes. After one night of curing at room temperature, the tubes were cut in order to obtain implants of 2 cm long.

Example 9: Synthesis of implants comprising barium sulfate in the core material

Typically, a mixture of 19.4 g of PDMS (base, medical grade) and 1 g, 2 g or 4 g of barium sulfate (5, 10 and 20% by weight, Aldrich) was transferred into a sterile container in a laminar flow hood. The mixture was homogenized with a spatula and placed at -20°C for 1 hour. Tubes comprising EVA (10% by weight of vinyl acetate, thickness of the wall 200 μm) were washed with water, dried and sterilized by UV in a laminar flow hood. Then, 0.5 g of SiOP₄ and 0.1 g of SnOct₂ were mixed together in a separate glass container. The mixture of the catalyst and the cross-linker was then added into the cold PDMS-barium sulfate mixture inside a laminar flow hood. After mixing the catalyst-cross-linker and the PDMS-barium sulfate, the mixture was injected in the EVA tubes. The ends of the tube were closed with a parafilm and left for one night in the laminar flow hood. After polymerization, the tubes were cut in order to obtain implants of 2 cm long. The implant extremities were closed with MED-2000 adhesive silicone (Nusil technology, Carpinteria, CA, USA).

Example 10: Synthesis of implants comprising anastrozole as active ingredient and barium sulfate in the core material according to an embodiment of the invention

Typically, a mixture of 19.4 g of PDMS (base, medical grade), 19.5 g of freshly ground anastrozole (API chemicals Limited, Abingdon, United Kingdom) and 2 g, 4 g or 8 g of BaSO₄ (5, 10 and 20% by weight of barium sulfate, Aldrich) was transferred into a sterile container in a laminar flow hood. The mixture was homogenized with a spatula and placed at -20°C for 1 hour. Tubes comprising EVA (10% by weight of vinyl acetate, internal diameter of 3 mm, thickness of the wall 200 μm and 15 cm long) were washed with water, dried and sterilized by UV in a laminar flow hood. After mixing the catalyst-cross-linker and the PDMS-anastrozole-barium sulfate as described above, the mixture was injected in the EVA tubes. After polymerization, the tubes were cut in order to obtain implants of 2 cm long. The implant extremities were closed with MED-2000 adhesive silicone (Nusil technology, Carpinteria, CA, USA).

Example 11: Synthesis of implants comprising anastrozole as active ingredient and barium sulfate in the sealant according to an embodiment of the invention

Typically, 19.4 g of PDMS (base, medical grade) and 19.5 g of freshly ground anastrozole (API Chemicals Limited, Abingdon, United Kingdom) was transferred into a sterile container before homogenizing the mixture with an ultraturrax T 25 basic (Ika, Staufen,
Germany). The blend was placed at -20°C for 1 hour. Then, 0.5 g of tetrapropyl orthosilicate (SiOP₄, cross-linker, medical grade) and 0.1 g of tin octoate (SnOct₂, catalyst, medical grade) were mixed together in a separate glass container. The mixture of the catalyst and the cross-linker was then added into the cold PDMS mixture inside a laminar flow hood. The PDMS-anastrozole-cross-linker-catalyst mixture was manually homogenized for 2 minutes before being placed under vacuum during 5 minutes in order to remove the air bubbles trapped in the blend. The PDMS mixture was finally transferred into a plastic syringe and kept at -20°C for at least 1 hour.

Typically, ethylene vinyl acetate (EVA) tubes were prepared by extrusion of EVA pellets (Elvax 3129, Dupont) into molds. The PDMS mixture was then injected into an EVA tube comprising 10% by weight of vinyl acetate (internal diameter of 3 mm, thickness of the wall 200 µm and 15 cm long) in a laminar flow hood. The ends of the tube were closed with a parafilm. After one night of curing at room temperature, the tubes were cut in order to obtain implants of 2 cm long. MED-2000 adhesive silicone (Nusil technology, Carpinteria, CA, USA) was mixed with increasing amounts of BaSO₄ (20% and 50% by weight). The implant extremities were closed with the MED-2000 mixtures. The implants were then moved in a Vismara 65 vacuum oven at 950 mbar for 4 hours at room temperature with the purpose to remove the propanol formed during the PDMS cross-linking.

Example 12: Radiopacity of the implants

Implants comprising barium sulfate in the core material:

PDMS implants comprising barium sulfate in the core material (5, 10 and 20% by weight) were prepared as in example 9. Typically, 19.4 g of PDMS (base, medical grade) and 1 g, 2 g or 4 g of BaSO₄ (Aldrich) were transferred into a sterile container before homogenizing the mixture with a stainless spatula. The blend was placed at -20°C for 1 hour. Then, 0.5 g of tetrapropyl orthosilicate (SiOP₄, cross-linker, medical grade) and 0.1 g of tin octoate (SnOct₂, catalyst, medical grade) were mixed together in a separate glass container. The mixture of the catalyst and the cross-linker was then added into the cold PDMS mixture inside a laminar flow hood. The PDMS-anastrozole-cross-linker-catalyst mixture was manually homogenized for 2 minutes before being placed under vacuum during 5 minutes in order to remove the air bubbles trapped in the blend. The PDMS mixture was finally transferred into a plastic syringe and kept at -20°C for at least 1 hour.

Typically, ethylene vinyl acetate (EVA) tubes were prepared by extrusion of EVA pellets (Elvax 3129, Dupont) in combination with blow molding. The PDMS mixture was then
injected into an EVA tube comprising 10% by weight of vinyl acetate (internal diameter of 3 mm, thickness of the wall 200 µm and 15 cm long) in a laminar flow hood. The ends of the tube were closed with a parafilm. After one night of curing at room temperature, the tubes were cut in order to obtain implants of 2 cm long. The implant extremities were closed with MED-2000 adhesive silicone (Nusil technology, Carpinteria, CA, USA). The implants were then moved in a Vismara 65 vacuum oven at 950 mbar for 4 hours at room temperature with the purpose to remove the propanol formed during the PDMS cross-linking.

*Implants comprising barium sulfate in the sealant:*

PDMS implants comprising barium sulfate in the sealant (20 and 50% by weight) were prepared as in example 11, but without the active ingredient. Typically, 19.4 g of polydimethylsiloxane (PDMS, base, medical grade) was placed in a sterile container and kept at -20°C for 1 hour. Then, 0.5 g of tetrapropyl orthosilicate (SIOPr4, cross-linker, medical grade) and 0.1 g of tin octoate (SnOct2, catalyst, medical grade) were mixed together in a separate glass container. The mixture of the catalyst and the cross-linker was then added into the cold PDMS inside a laminar flow hood. The PDMS-cross-linker-catalyst mixture was manually homogenized for 2 minutes before being placed under vacuum during 5 minutes in order to remove the air bubbles trapped in the blend. The PDMS mixture was finally transferred into a plastic syringe and kept at -20°C for at least 1 hour.

Typically, ethylene vinyl acetate (EVA) tubes were prepared by extrusion of EVA pellets (Elvax 3129, Dupont) in combination with blow molding. The PDMS mixture was then injected into an EVA tube comprising 10% by weight of vinyl acetate (internal diameter of 3 mm, thickness of the wall 200 µm and 15 cm long) in a laminar flow hood. The ends of the tube were closed with a parafilm. After one night of curing at room temperature, the tubes were cut in order to obtain implants of 2 cm long. MED-2000 adhesive silicone (Nusil technology, Carpinteria, CA, USA) was mixed with increasing amounts of BaSO4 (20 and 50% by weight). The implant extremities were closed with the MED-2000 mixtures. The implants were then moved in a Vismara 65 vacuum oven at 950 mbar for 4 hours at room temperature with the purpose to remove the propanol formed during the PDMS cross-linking.

*Radiopacity:*

Five types of implants were synthesized comprising 5, 10 or 20% of barium sulfate in the core material or comprising 20 or 50% of barium sulfate in the sealant and were X-rayed.
Figure 1 represents an X-ray image of an implant 1 comprising 20% of barium sulfate in the sealant, of an implant 2 comprising 50% of barium sulfate in the sealant, of an implant 3 comprising 5% of barium sulfate in the core material and of an implant 4 comprising 10% of barium sulfate in the core material. Figure 2 represents an X-ray image of in vitro implant 5 comprising 20% of barium sulfate in the sealant and of an implant 6 comprising 20% of barium sulfate in the core material.

The radiopacity of the implants was tested in vivo in cynomolgus monkeys. Abdominal incisions were made and 2 implants were inserted without fixation. One implant was placed at the right side and one implant was placed at the left side, after which the skin was sutured. Figures 3 represent X-ray images of an implant 7 comprising 50% of barium sulfate in the sealant, placed at the right side and of an implant 8 comprising 20% of barium sulfate in the sealant, placed at the left side. Figure 3A represents a front view of the animal on day 0. Figure 3B represents a side view of the animal on day 0. Figures 4 represent X-ray images of an implant 9 comprising 20% of barium sulfate in the core material, placed at the right side and of an implant 10 comprising 50% of barium sulfate in the sealant, placed at the left side. Figure 4A represents a front view of the animal on day 0. Figure 4B represents a side view of the animal on day 0. Figure 4C represents a front view of the animal after 2 months. Figure 4D represents a side view of the animal after 2 months. Figures 5 represent X-ray images of 2 implants without barium sulfate, an implant 11 comprising 5% of barium sulfate in the core material, an implant 12 comprising 10% of barium sulfate in the core material and of an implant 13 comprising 20% of barium sulfate in the core material. Figure 5A represents a front view of the animal on day 0. Figure 5B represents a side view of the animal on day 0. The implants comprising barium sulfate in the core material or sealant were visible. The implants without barium sulfate were not detected.

**Example 13:** Effect on the release of anastrozole by using MED-2000 adhesive silicone as a sealant

Implants comprising anastrozole as an active ingredient were prepared as described in example 5, but with and without MED-2000 adhesive silicone as a sealant. Implants were tested for the release of anastrozole without a sealant and with MED-2000 adhesive silicone as a sealant. Furthermore, the implants comprised an EVA tube comprising 10% by weight of vinyl acetate and a thickness of 0.1 mm, 0.2 mm or 0.3 mm. In order to determine the kinetics of the release of anastrozole, the implants were placed in sealed tubes comprising 100 ml of phosphate buffer pH 7.4. The tubes were placed in a bath at 37°C and 140 rpm. The measurements were performed during 400 days for the implants
without a sealant and during more than 500 days for the implants with MED-2000 adhesive silicone as a sealant. Figure 6A represents the mean release of anastrozole per 24h as a function of time for implants without a sealant. The results show that during the first 5 days an important quantity of anastrozole is released from the implants followed by a decreasing quantity of released anastrozole per 24h as a function of time. Figure 6B represents the mean release of anastrozole per 24h as a function of time for implants with MED-2000 adhesive silicone as a sealant. The results show that the release of anastrozole from the implants is constant during time for more than 400 days.

Example 14: Effect of sterilization on the release of anastrozole

Implants were prepared as in example 5. Two series of 3 implants were sterilized with ethylene oxide in order to see if sterilization influenced the release of the active principle. Sterilization was performed before placing the implants in the sealed tubes comprising 100 ml of phosphate buffer pH 7.4. The tubes were placed in a bath at 37°C and 140 rpm. The measurements were performed during 14 days. Figure 7 illustrates the mean release of anastrozole per 24h as a function of time for sterilized and non-sterilized implants with MED-2000 adhesive silicone as a sealant. The results show that the sterilization has no significant effect on the release of anastrozole.

Example 15: Release of celecoxib from implants with or without a sealant:

Three series of 3 implants were prepared, the first series was implant without sealant, the second was implant with EVA as a sealant and the last one was implants with PDMS as a sealant in order to see if the sealant influenced the release of the active ingredient. The implants were placed in the sealed tubes comprising 100 ml of phosphate buffer pH 7.4. The tubes were placed in a bath at 37°C and 140 rpm. The measurements were performed during 38 days. Figure 8A illustrates the mean release of celecoxib per 24h as a function of time for implant without sealant. Figure 8B illustrates the mean release of celecoxib per 24h as a function of time for implant with EVA as a sealant. Figure 8C illustrates the mean release of celecoxib per 24h as a function of time for implant with PDMS as a sealant.

The results show that the sealant has significant effect on the release of Celecoxib and that PDMS sealant can reduce the burst effect and controlled the liberation of the celecoxib.

Example 16: Effect of the composition of the tube on the release of celecoxib

Implants were prepared comprising PDMS as a core material and celecoxib as an active ingredient without a tube or with an EVA tube comprising 18% or 28% by weight of vinyl
acetate and with MED-2000 adhesive silicone as a sealant. In order to determine the kinetics of the release of celecoxib, the implants were placed in sealed tubes comprising 100 ml of phosphate buffer pH 7.4. The tubes were placed in a bath at 37°C and 140 rpm. The measurements were performed during 400 days for all implants tested. Figures 9A and 9B represent the mean release of celecoxib per 24h as a function of time for implants without a tube and with an EVA tube comprising 18% or 28% by weight of vinyl acetate. The results show that the release of celecoxib is constant for more than 300 days for implants with an EVA tube comprising 28% by weight of vinyl acetate. The release of celecoxib is also constant for more than 300 days for implants with an EVA tube comprising 18% by weight of vinyl acetate. The results show that the implants comprising 18% by weight of vinyl acetate release a lower amount of celecoxib per day compared with implants with an EVA tube comprising 28% by weight of vinyl acetate. The implants without an EVA tube show an exponential decrease in the release of celecoxib.

Example 17: Pharmacokinetic study of implants comprising a PDMS core and celecoxib as active ingredient in Wistar rats

Implants comprising celecoxib as active ingredient were synthesized as described in example 6. 28 of these implants were placed intraperitoneal in Wistar rats and 28 were placed subcutaneous in Wistar rats. One implant was used per rat. Pharmacokinetics was observed for more than 6 months. Six rats were used to determine the concentration of celecoxib in the serum. The concentration of celecoxib in the serum was determined every day during the first week, 2 times per week during the next 3 weeks and once per week during the following weeks of the study. At every time point, two rats were sampled. 16 rats were used to measure the concentration of celecoxib in the peritoneal cavity. The peritoneal concentration of celecoxib was assayed on day 1, day 4 and once per month during the next months of the study. At every time point, 2 rats were sampled and sacrificed. The peritoneal concentration of celecoxib was determined in a 1 ml sample obtained after washing the peritoneal cavity with 1 ml of phosphate buffer pH 7.4. The results shown in Figure 10 demonstrate that the active ingredient celecoxib is liberated in a controlled way during more than 6 months. Figure 10A illustrates the concentration of celecoxib in serum as a function of the number of days after implantation. No differences in the concentration of celecoxib in the serum were observed between rats receiving the implant intraperitoneal and rats receiving the implant subcutaneous. Figure 10B illustrates the concentration of celecoxib in peritoneal liquid as a function of the number of days after implantation. The results show that the concentration of celecoxib in the peritoneal liquid
is higher when the implant is delivered intraperitoneally compared with subcutaneous implantation.

Furthermore, the concentration of metabolites of celecoxib was studied. Six rats were used to determine the concentration of the metabolites of celecoxib in the serum. The concentration of the metabolites of celecoxib in the serum was determined every day during the first week, 2 times per week during the next 3 weeks and once per week during the following weeks of the study. At every time point, two rats were sampled. Sixteen rats were used to measure the concentration of the metabolites of celecoxib in the peritoneal cavity. The peritoneal concentration of the metabolites of celecoxib was assayed on day 3 and once per month during the next months of the study. At every time point, 1 or 2 rats were sampled and sacrificed. The peritoneal concentration of the metabolites of celecoxib was determined in a 1 ml sample obtained after washing the peritoneal cavity with 1 ml of phosphate buffer pH 7.4.

Without being bound to theory, Figure 14 represents a proposed metabolic pathway for celecoxib in rats (Paulson et al. Drug Metab. Dispos. 2000; 28(5):514521), and references to some of the metabolites is made hereafter. Figure 15 shows that celecoxib is metabolized in rats and that the metabolite HO-celecoxib is present in the rats during more than two years. Figure 15A shows the concentration of HO-celecoxib in serum of rats as a function of the number of days after implantation. No differences in the concentration of HO-celecoxib in the serum were observed between rats receiving the implant intraperitoneal and rats receiving the implant subcutaneous. Figure 15B shows the concentration of HO-celecoxib in peritoneal liquid (PL) of rats as a function of the number of days after implantation. The results indicate a tendency to a higher concentration of HO-celecoxib in the peritoneal liquid when the implant is delivered intraperitoneally compared with subcutaneous implantation.

Figures 16A and 17A show the concentration of HOOC-celecoxib 1 and HOOC-celecoxib 2 respectively (cis/trans isomers of HOOC-celecoxib), in serum of rats as a function of the number of days after implantation. Figures 16B and 17B show the concentration of HOOC-celecoxib 1 and HOOC-celecoxib 2 respectively, in peritoneal liquid (PL) of rats as a function of the number of days after implantation. These results show that that celecoxib is metabolized in rats and that the metabolite HOOC-celecoxib is present in the rats during more than two years. No differences in the concentration of the metabolite HOOC-celecoxib in the serum and in the PF were observed between rats receiving the implant intraperitoneal and rats receiving the implant subcutaneous.
**Example 18:** Pharmacokinetic study of implants comprising a PDMS core and anastrozole as active ingredient in Wistar rats

Implants comprising anastrozole as active ingredient were synthesized as described in example 5. 28 of these implants were placed intraperitoneal in Wistar rats and 28 were placed subcutaneous in Wistar rats. One implant was used per rat. Pharmacokinetics was observed for more than 6 months. Six rats were used to determine the concentration of anastrozole in the serum. The concentration of anastrozole in the serum was determined every day during the first week, 2 times per week during the next 3 weeks and once per week during the following weeks of the study. At every time point, 2 rats were sampled. 16 rats were used to measure the concentration of anastrozole in the peritoneal cavity. The peritoneal concentration of anastrozole was assayed on day 1, day 4 and once per month during the next months of the study. At every time point, 2 rats were sampled and sacrificed. The peritoneal concentration of anastrozole was determined in a 1 ml sample obtained after washing the peritoneal cavity with 1 ml of phosphate buffer pH 7.4. Figure 11A illustrates the concentration of anastrozole in serum as a function of the number of days after intraperitoneal implantation. The results demonstrate that the concentration of anastrozole is constant for more than 6 months in the serum of rats after intraperitoneal implantation. Figure 11B illustrates the concentration of anastrozole in peritoneal fluid as a function of the number of days after intraperitoneal implantation. The results demonstrate that the concentration of anastrozole is constant for 6 months in the peritoneal fluid of rats after intraperitoneal implantation.

**Example 19:** Pharmacokinetic study of implants comprising a PDMS core and celecoxib or anastrozole as active ingredient in cynomolgus monkeys

Implants comprising anastrozole or celecoxib as active ingredient were prepared as described in examples 5 and 6. Two cynomolgus monkeys received each two implants comprising celecoxib and 2 cynomolgus monkeys received each two implants comprising anastrozole. Pharmacokinetics was observed for more than 5 months for celecoxib and for more than 10 months for anastrozole. The concentration of the active ingredient in the serum was determined every 3 days during the first week, once per week during the next 3 months and once per month during the remainder of the study. Figure 12A illustrates the concentration of celecoxib in the serum as a function of the number of days after implantation. Figure 12B illustrates the concentration of anastrozole in serum as a function of the number of days after implantation. The results show that the implants comprising anastrozole or celecoxib effectively liberate their active ingredient in a controlled way during the desired period.
Example 20: Analysis of the remaining amounts of anastrozole in the implants in vivo

Implants comprising anastrozole as active ingredient were prepared as described in examples 5. The implants were placed subcutaneous or intraperitoneal and the remaining amounts of anastrozole in the implants were determined at different time points after implantation. Figure 13 demonstrates the remaining amounts of anastrozole in the implants placed subcutaneous or intraperitoneal. The result shows that the amount of anastrozole in the implants placed subcutaneous or intraperitoneal after 180 days was still satisfying; suggesting that a long term delivery of the active ingredient is possible.
CLAIMS

1. An implant comprising:
   - a core material comprising polydimethylsiloxane or at least one hydrogel polymer;
   - a tube encasing said core material comprising an ethylene vinyl acetate polymer or at least one hydrogel polymer;
   - a sealant for closure of the open ends of said tube comprising polydimethylsiloxane or a mono-, di-, or triacetoxy derivative thereof, or at least one hydrogel polymer; and
   - at least one active ingredient;

wherein said at least one active ingredient is selected from the group comprising celecoxib, sulindac, tamoxifen, oestrogen, oestradiol, ethinyl oestradiol, mestranol, dienogest, norgestrel, levonorgestrel, desogestrel, norgestimate, ethynodiol diacetate, leuprorelin, buserelin, gonrelin, triptorelin, nafarelin, deslorelin, histrelin, and supprelin; and

with the proviso that when the sealant is said at least one hydrogel polymer, the core material comprises polydimethylsiloxane.

2. The implant according to claim 1, wherein said implant comprises an inert metal coating and/or at least one radiopaque material, preferably said implant comprises at least 0.01% by weight of an inert metal coating and/or at least 0.01% of at least one radiopaque material.

3. The implant according to claim 2, wherein said radiopaque material is selected from the group comprising barium, gold, platinum, tantalum, bismuth and iodine or salts thereof, or a radiopaque polymer, preferably said radiopaque material is barium sulfate.

4. The implant according to claim 2, wherein said inert metal is selected from the group comprising silver, gold, titanium, tungsten, barium, bismuth, platinum and palladium.

5. The implant according to any one of claims 1 to 4, wherein said at least one active ingredient is selected from the group comprising celecoxib, sulindac and dienogest.

6. The implant according to any one of claim 1 to 5, wherein said core material comprises polydimethylsiloxane, wherein said tube encasing said core material comprises an ethylene vinyl acetate polymer; and wherein said sealant for closure of
the open ends of said tube comprises polydimethylsiloxane or a mono-, di-, or triacetoxy derivative thereof.

7. The implant according to any one of claim 1 to 5, wherein said core material comprises polydimethylsiloxane, wherein said tube encasing said core material comprises at least one hydrogel polymer; and wherein said sealant for closure of the open ends of said tube comprises polydimethylsiloxane or a mono-, di-, or triacetoxy derivative thereof.

8. The implant according to any one of claims 1 to 7, wherein said implant comprises from about 40% to about 75% by weight of said at least one active ingredient.

9. The implant according to any one of claims 1 to 8, for use as a medicament.

10. The implant according to any of claims 1 to 9, for use in the treatment of endometriosis.

11. The implant according to any one of claims 9 or 10, wherein said implant is administered intraperitoneally or subcutaneously.

12. The implant according to any one of claims 9 to 10, wherein said implant is administered once per 180 days, or less frequently, preferably once per year, or less frequently.
Thickenes of coated polymer

**FIG 6A**

**FIG 6B**
FIG 13

- $y = -0.0384x + 74.97$
- $y = -0.019x + 70$

- Subcutaneous
- IP
- Linear (IP)
- Linear (subcutaneous)
FIG 14
## A. CLASSIFICATION OF SUBJECT MATTER

<table>
<thead>
<tr>
<th>INV.</th>
<th>A61K9/00</th>
<th>A61K31/19</th>
<th>A61K31/415</th>
<th>A61K31/4196</th>
<th>A61K31/565</th>
</tr>
</thead>
</table>

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

**Minimum documentation searched (classification system followed by classification symbols)**

A61K

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

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
</table>
|          | examples 1-29
|          | column 4, line 5 - line 25                                                      | 1-12                 |
| Y        | US 3 854 480 A (ZAFFARONI A) 17 December 1974 (1974-12-17)                     | 1,9,11               |
|          | column 7, line 59 - column 8, line 32                                           | 1-12                 |
|          | claims 1-11
|          | column 5, line 48 - column 6, line 40                                           |                      |
| X        | WO 00/28967 A1 (LEIRAS OY [FI]; MARKKULA TOMMI [GB]; ALA SORVARI JAHA [FI]; JUKARAINEN) 25 May 2000 (2000-05-25) | 1,9,11               |
| Y        | page 17, line 2 - page 18, line 10                                              | 1-12                 |
|          | -----                                                                            |                      |

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

<table>
<thead>
<tr>
<th>Special categories of cited documents :</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;A*&quot; document defining the general state of the art which is not considered to be of particular relevance</td>
</tr>
<tr>
<td>&quot;E*&quot; earlier document but published on or after the international filing date</td>
</tr>
<tr>
<td>&quot;L*&quot; document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another olation or other special reason (as specified)</td>
</tr>
<tr>
<td>&quot;O*&quot; document referring to an oral disclosure, use, exhibition or other means</td>
</tr>
<tr>
<td>&quot;P*&quot; document published prior to the international filing date but later than the priority date claimed</td>
</tr>
</tbody>
</table>

| Later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention |
| "X*" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone |
| "Y*" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art |
| "S*" document member of the same patent family |

Date of the actual completion of the international search: 19 March 2012

Date of mailing of the international search report: 29/03/2012

Name and mailing address of the IBA/
European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk
Tel: (+31-70) 340-2040, Fax: (+31-70) 340-3016

Authorized officer:
Sindel, Ulrike
<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
</table>

Form PCT/ISA/5 (continuation of second sheet) [April 2005]
<table>
<thead>
<tr>
<th>Patent document cited in search report</th>
<th>Publication date</th>
<th>Patent family member(s)</th>
<th>Publication date</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>CA 2161950 A1</td>
<td>03-05-1996</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DE 69522409 D1</td>
<td>04-10-2001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DE 69522409 T2</td>
<td>13-12-2001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DK 710491 T3</td>
<td>08-10-2001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP 0710491 A1</td>
<td>08-05-1996</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ES 2160675 T3</td>
<td>16-11-2001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PT 710491 E</td>
<td>28-12-2001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 5660848 A</td>
<td>26-08-1997</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 5756115 A</td>
<td>26-05-1998</td>
</tr>
<tr>
<td>US 3854480 A 17-12-1974</td>
<td></td>
<td>CH 574742 A5</td>
<td>30-04-1976</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DE 2135533 A1</td>
<td>01-02-1973</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FR 2143564 A1</td>
<td>09-02-1973</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 3854480 A</td>
<td>17-12-1974</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AT 241338 T</td>
<td>15-06-2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AU 769229 B2</td>
<td>22-01-2004</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AU 1048700 A</td>
<td>05-06-2000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BG 65009 B1</td>
<td>29-12-2006</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BR 9915327 A</td>
<td>09-10-2001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CA 2351064 A1</td>
<td>25-05-2000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CN 1367682 A</td>
<td>04-09-2002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CO 5170475 A1</td>
<td>27-06-2002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CZ 2601157 A3</td>
<td>12-09-2001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DE 69908399 D1</td>
<td>03-07-2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DE 69908399 T2</td>
<td>05-02-2004</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DK 1128810 T3</td>
<td>15-09-2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EE 200100255 A</td>
<td>16-12-2002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP 1128810 A1</td>
<td>05-09-2001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ES 2201794 T3</td>
<td>16-03-2004</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HU 0202666 A2</td>
<td>28-12-2002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ID 29339 A</td>
<td>23-08-2001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IL 142524 A</td>
<td>31-12-2006</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 2003521456 A</td>
<td>15-07-2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NO 20012046 A</td>
<td>28-06-2001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NZ 511214 A</td>
<td>29-04-2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PL 356658 A1</td>
<td>28-06-2004</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PT 1128810 E</td>
<td>30-09-2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RU 2226388 C2</td>
<td>10-04-2004</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SK 5152001 A3</td>
<td>08-10-2001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>UA 64821 C2</td>
<td>17-09-2001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 6117442 A</td>
<td>12-09-2000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ZA 200103299 A</td>
<td>13-05-2002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AT 223733 T</td>
<td>15-09-2002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BR 9902528 A</td>
<td>02-05-2000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CA 2276587 A1</td>
<td>02-01-2000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DE 69902852 D1</td>
<td>17-10-2002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DE 69902852 T2</td>
<td>16-01-2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DK 970704 T3</td>
<td>20-01-2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ES 2186280 T3</td>
<td>01-05-2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HU 9902225 A2</td>
<td>28-01-2002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 4713700 B2</td>
<td>29-06-2011</td>
</tr>
<tr>
<td>Patent document cited in search report</td>
<td>Publication date</td>
<td>Patent family member(s)</td>
<td>Publication date</td>
</tr>
<tr>
<td>---------------------------------------</td>
<td>-----------------</td>
<td>-------------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>JP 2000044489 A</td>
<td>15-02-2000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PT 970704 E</td>
<td>31-01-2003</td>
<td></td>
<td></td>
</tr>
<tr>
<td>US 6117441 A</td>
<td>12-09-2000</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>AT 344018 T</td>
<td>15-11-2006</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AU 1969697 A</td>
<td>10-09-1997</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BR 9707637 A</td>
<td>27-07-1999</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CA 2243274 A</td>
<td>28-08-1997</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DE 69732176 D1</td>
<td>10-02-2005</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DE 69732176 T2</td>
<td>11-05-2006</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DE 69736911 T2</td>
<td>14-06-2007</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DK 881891 T3</td>
<td>23-05-2005</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DK 1488784 T3</td>
<td>05-03-2007</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP 0881891 A1</td>
<td>09-12-1998</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ES 2236793 T3</td>
<td>16-07-2005</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ES 2274367 T3</td>
<td>16-05-2007</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 2000505419 A</td>
<td>09-05-2000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PT 881891 E</td>
<td>29-04-2005</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PT 1488784 E</td>
<td>29-12-2006</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 5733565 A</td>
<td>31-03-1998</td>
</tr>
<tr>
<td></td>
<td></td>
<td>WO 9730656 A1</td>
<td>28-08-1997</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CA 1212869 A1</td>
<td>21-10-1986</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DE 3378303 D1</td>
<td>01-12-1988</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DK 514383 A</td>
<td>10-11-1983</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP 0089782 A1</td>
<td>28-09-1983</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FI 834150 A</td>
<td>11-11-1983</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IL 68073 A</td>
<td>20-10-1987</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NO 834072 A</td>
<td>08-11-1983</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NZ 203531 A</td>
<td>09-05-1986</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 4535485 A</td>
<td>20-08-1985</td>
</tr>
<tr>
<td></td>
<td></td>
<td>WO 8303193 A1</td>
<td>29-09-1983</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ZA 8301586 A</td>
<td>30-11-1983</td>
</tr>
</tbody>
</table>