

(12) STANDARD PATENT
(19) AUSTRALIAN PATENT OFFICE

(11) Application No. **AU 2007287098 C1**

(54) Title
Methods and compositions for treating cancer

(51) International Patent Classification(s)
A61P 35/00 (2006.01) **A61K 45/06** (2006.01)
A61K 31/58 (2006.01)

(21) Application No: **2007287098** (22) Date of Filing: **2007.08.23**

(87) WIPO No: **WO08/024484**

(30) Priority Data

(31)	Number	(32)	Date	(33)	Country
	60/921,506		2006.08.25		US

(43) Publication Date: **2008.02.28**

(44) Accepted Journal Date: **2013.08.15**

(44) Amended Journal Date: **2018.03.15**

(71) Applicant(s)
Janssen Oncology, Inc.

(72) Inventor(s)
Auerbach, Alan H.;Belldegrun, Arie S.

(74) Agent / Attorney
Shelston IP Pty Ltd., L 21 60 Margaret St, Sydney, NSW, 2000, AU

(56) Related Art
O'DONNELL A ET AL, BRITISH JOURNAL OF CANCER VOL 90, NO 12, 14 JUNE
2004, PAGES 2317-2325
US2006/030608
WO2004/037269
WO2002/053138

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
28 February 2008 (28.02.2008)

PCT

(10) International Publication Number
WO 2008/024484 A1

(51) International Patent Classification:

A61P 35/00 (2006.01) A61K 45/06 (2006.01)
A61K 31/58 (2006.01)

(21) International Application Number:

PCT/US2007/018769

(22) International Filing Date: 23 August 2007 (23.08.2007)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/921,506 25 August 2006 (25.08.2006) US

(71) Applicant (for all designated States except US):

COUGAR BIOTECHNOLOGY, INC. [US/US]; 10990
Wilshire Blvd., Suite 1200, Los Angeles, CA 90024 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): AUERBACH,
Alan, H. [US/US]; 10990 Wilshire Blvd., Los Angeles,
CA 90024 (US). BELLDEGRUN, Arie, S. [US/US];
10990 Wilshire Blvd., Los Angeles, CA 90024 (US).

(74) Agents: INSOGNA, Anthony, M. et al.; Jones Day, 222
East 41st Street, New York, NY 10017-6702 (US).

(81) Designated States (unless otherwise indicated, for every
kind of national protection available): AE, AG, AL, AM,
AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH,
CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG,
ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL,
IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK,
LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW,
MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL,
PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY,
TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA,
ZM, ZW.

(84) Designated States (unless otherwise indicated, for every
kind of regional protection available): ARIPO (BW, GH,
GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM,
ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI,
FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL,
PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM,
GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

- with international search report
- before the expiration of the time limit for amending the
claims and to be republished in the event of receipt of
amendments

(54) Title: METHODS AND COMPOSITIONS FOR TREATING CANCER

(57) Abstract: Methods and compositions for treating cancer are described herein. More particularly, the methods for treating cancer comprise administering a 17α -hydroxylase/C₁₇, 20-lyase inhibitor, such as abiraterone acetate (i.e., 3β -acetoxy-17-(3-pyridyl) androsta-5, 16-diene), in combination with at least one additional therapeutic agent such as an anti-cancer agent or a steroid. Furthermore, disclosed are compositions comprising a 17α -hydroxylase/C₁₇, 20-lyase inhibitor, and at least one additional therapeutic agent, such as an anti-cancer agent or a steroid.



WO 2008/024484 A1

METHODS AND COMPOSITIONS FOR TREATING CANCER

FIELD OF THE INVENTION

[0001] Methods and compositions for treating cancer are described herein. More particularly, the methods for treating cancer comprise administering a 17 α -hydroxylase/C₁₇,₂₀-lyase inhibitor, such as abiraterone acetate (*i.e.*, 3 β -acetoxy-17-(3-pyridyl) androsta-5, 16-diene), in combination with at least one additional therapeutic agent, such as an anti-cancer agent or a steroid. Furthermore, disclosed are compositions comprising a 17 α -hydroxylase/C₁₇,₂₀-lyase inhibitor, and at least one additional therapeutic agent such as an anti-cancer agent or a steroid, *e.g.*, a corticosteroid or, more specifically, a glucocorticoid.

BACKGROUND

[0002] The number of people diagnosed with cancer has significantly increased. Of special interest are individuals diagnosed with androgen-dependent disorders, such as prostate cancer, and estrogen-dependent disorders, such as breast cancer since such diagnoses are increasing in number at an alarming rate.

[0003] Prostate cancer is currently the most common non-skin cancer and the second leading cause of cancer-related death in men after lung cancer. The primary course of treatment for patients diagnosed with organ-confined prostate cancer is usually prostatectomy or radiotherapy. Not only are these treatments highly invasive and have undesirable side effects, such localized treatments are not effective on prostate cancer after it has metastasized. Moreover, a large percent of individuals who receive localized treatments will suffer from recurring cancer.

[0004] Additionally, breast cancer incidence in women has increased from one out of every 20 women in 1960 to one out of every eight women in 2005. Moreover, it is the most common cancer among white and African-American women. Similar to treating prostate cancer, most options for women diagnosed with breast cancer are highly invasive and have significant side-effects. Such treatments include surgery, radiation and chemotherapy.

[0005] Hormone therapy is another treatment option for individuals diagnosed with prostate or breast cancer. Hormone therapy is a form of systemic treatment for prostate or breast cancer wherein hormone ablation agents are used to suppress the production or block

the effects of hormones, such as estrogen and progesterone in the body, which are believed to promote the growth of breast cancer, as well as testosterone and dihydrotestosterone, which are believed to promote the growth of prostate cancer. Moreover, hormone therapy is less invasive than surgery and does not have many of the side effects associated with chemotherapy or radiation. Hormone therapy can also be used by itself or in addition to localized therapy and has shown to be effective in individuals whose cancer has metastasized.

[0006] Even though hormone therapy is less invasive and can be used on more advanced stages of cancer, some individuals administered current hormone therapy treatments may not show a significant response or may not show any response at all to such treatments. Additionally, some patients treated with current hormone therapy treatments may also suffer from relapsing or recurring cancer. Currently, such refractory cancer patients are left with very few treatment options.

[0007] Despite the progress made in the treatment of cancer, there remains a need for more effective ways to treat cancer such as, but not limited to, prostate cancer and breast cancer. Additionally, there is a need for effective anti-cancer treatment options for patients who are not responding to current anti-cancer treatments. Also, there is a need for effective anti-cancer treatment options for patients whose cancer has recurred.

SUMMARY OF THE INVENTION

[0008] Accordingly, in one aspect the present invention provides a use of a therapeutically effective amount of abiraterone acetate or a pharmaceutically acceptable salt thereof in the preparation of a medicament for the treatment of a prostate cancer in a human, wherein the medicament is administered in addition to a therapeutically effective amount of prednisone.

[0008a] In another aspect, the present invention provides a compound for use in the treatment of a prostate cancer in a human, wherein the compound is a therapeutically effective amount of abiraterone acetate or a pharmaceutically acceptable salt thereof, and

wherein the compound is administered in addition to a therapeutically effective amount of prednisone.

[0008b] In a further aspect, the present invention provides a use of a therapeutically effective amount of abiraterone acetate or a pharmaceutically acceptable salt thereof in the preparation of a medicament for the treatment of a refractory prostate cancer in a human, wherein the medicament is administered in addition to a therapeutically effective amount of prednisone.

[0008c] In yet a further aspect, the present invention provides a compound for use in the treatment of a refractory prostate cancer in a human, wherein the compound is a therapeutically effective amount of abiraterone acetate or a pharmaceutically acceptable salt thereof, and wherein the compound is administered in addition to a therapeutically effective amount of prednisone.

[0008d] In yet a further aspect, the present invention provides a use of about 50 mg/day to about 2000 mg/day of abiraterone acetate in the preparation of a medicament for the treatment of a prostate cancer in a human, wherein the medicament is administered in addition to about 10 mg/day to about 250 mg/day of prednisone.

[0008e] In yet a further aspect, the present invention provides abiraterone acetate for use in the treatment of a prostate cancer in a human, wherein the abiraterone acetate is administered in an amount of about 50 mg/day to about 2000 mg/day, and wherein the abiraterone acetate is prepared to be administered in addition to about 10 mg/day to about 250 mg/day of prednisone.

[0008f] In yet another further aspect, the present invention provides a pharmaceutical composition for use in the treatment of a prostate cancer in a human comprising a therapeutically effective amount of abiraterone acetate or a pharmaceutically acceptable salt thereof and a therapeutically effective amount of prednisone.

[0008g] Preferably, the therapeutically effective amount of the abiraterone acetate or pharmaceutically acceptable salt thereof is from about 50 mg/day to about 2000 mg/day.

[0008h] Preferably, the refractory prostate cancer is not responding to at least one anti-cancer agent.

[0008i] Preferably, the therapeutically effective amount of the abiraterone acetate or pharmaceutically acceptable salt thereof is from about 50 mg to about 500 mg and the therapeutically effective amount of prednisone is from about 0.25 mg to about 3.5 mg; wherein said composition is suitable for oral administration.

[0008j] Described herein are methods for treating a cancer in which a therapeutically effective amount of a 17α -hydroxylase/ $17,20$ -lyase inhibitor, such as abiraterone acetate (*i.e.* 3β -acetoxy- 17 -(3-pyridyl)androsta- $5,16$ -diene), is administered to a patient, *e.g.*, a patient in need thereof, in combination with a therapeutically effective amount of at least one additional therapeutic agent including, but not limited to, an anti-cancer agent or steroid. Such methods can also provide an effective treatment for individuals with a refractory cancer, including individuals who are currently undergoing a cancer treatment. Therefore, in certain embodiments, the method is directed to treating a refractory cancer in a patient, in which a therapeutically effective amount of 17α -hydroxylase/ $17,20$ -lyase inhibitor is administered to a patient currently receiving an anti-cancer agent.

[0009] For example, in certain embodiments, the method for the treatment of a cancer in a mammal comprises administering an amount of about 0.01 mg/kg/day to about 100 mg/kg/day of abiraterone acetate and an amount of about 0.1 mg/m² to about 20 mg/m² of mitoxantrone.

[0010] In another preferred embodiment, the method for the treatment of a cancer in a mammal comprises administering an amount of about 0.01 mg/kg/day to about 100 mg/kg/day of abiraterone acetate and an amount of about 1 mg/m² to about 175 mg/m² of paclitaxel.

[0011] In still another preferred embodiment, the method for the treatment of a cancer in a mammal comprises administering an amount of about 0.01 mg/kg/day to about

100 mg/kg/day of abiraterone acetate and an amount of about 1 mg/m² to about 100 mg/m² of docetaxel.

[0012] Furthermore, described herein is a method for the treatment of a cancer in a mammal comprising administering an amount of about 0.01 mg/kg/day to about 100 mg/kg/day of abiraterone acetate; and an amount of about 0.01 mg to about 200 mg of leuprolide, wherein the leuprolide is administered over a period of about 3 days to about 12 months.

[0013] In other preferred embodiments, the method for the treatment of a cancer in a mammal comprises administering an amount of about 0.01 mg/kg/day to about 100 mg/kg/day of abiraterone acetate and an amount of about 0.01 mg to about 20 mg of goserelin, wherein the goserelin is administered over a period of about 28 days to about 3 months.

[0014] Additionally, in another preferred embodiment, the method for the treatment of a cancer in a mammal comprises administering an amount of about 0.01 mg/kg/day to about 100 mg/kg/day of abiraterone acetate and an amount of about 0.01 mg to about 20 mg of triptorelin, wherein the triptorelin is administered over a period of about 1 month.

[0015] The method for the treatment of a cancer in a mammal can also comprise administering an amount of about 0.01 mg/kg/day to about 100 mg/kg/day of abiraterone acetate and an amount of about 0.1 µg/day to about 500 µg/day seocalcitol, such as about 100 µg/day of seocalcitol.

[0016] Also, the method for the treatment of a cancer in a mammal can comprise administering an amount of about 0.01 mg/kg/day to about 100 mg/kg/day of abiraterone acetate and an amount of about 1 mg/day to about 300 mg/day of bicalutamide.

[0017] In yet another embodiment, the method for the treatment of a cancer in a mammal can comprise administering an amount of about 0.01 mg/kg/day to about 100 mg/kg/day of abiraterone acetate and an amount of about 1 mg/day to about 2000 mg/day of flutamide.

[0018] deleted

[0019] Also described herein are compositions for the treatment of cancer that comprise a combination of a therapeutically effective amount of at least one 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor and a therapeutically effective amount of at least one additional anti-cancer agent, such as, but not limited to, mitoxantrone, paclitaxel, docetaxel, leuprolide, goserelin, triptorelin, seocalcitol, bicalutamide and flutamide.

[0020] Finally, single unit dosage forms comprising abiraterone acetate and a glucocorticoid, optionally with carriers, diluents or excipients, are contemplated. Also, kits comprising at least one 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor and an additional anti cancer agent or steroid are contemplated. For example, the kit may include a vial containing abiraterone acetate and another vial containing a glucocorticoid.

DEFINITIONS

[0021] As used herein and unless otherwise defined the word "cancer", refers to the growth, division or proliferation of abnormal cells in the body. Cancers that can be treated with the methods and the compositions described herein include, but are not limited to, prostate cancer, breast cancer, adrenal cancer, leukaemia, lymphoma, myeloma, Waldenström's macroglobulinemia, monoclonal gammopathy, benign monoclonal gammopathy, heavy chain disease, bone and connective tissue sarcoma, brain tumors, thyroid cancer, pancreatic cancer, pituitary cancer, eye cancer, vaginal cancer, vulvar cancer, cervical cancer, uterine cancer, ovarian cancer, oesophageal cancer, stomach cancer, colon cancer, rectal cancer, liver cancer, gallbladder cancer, cholangiocarcinoma, lung cancer, testicular cancer, penal cancer, oral cancer, skin cancer, kidney cancers, Wilms' tumor and bladder cancer.

[0022] As used herein, and unless otherwise defined, the terms "treat", "treating" and "treatment" include the eradication, removal, modification, management or control of a

tumor or primary, regional, or metastatic cancer cells or tissue and the minimization or delay of the spread of cancer.

[0023] As used herein, and unless otherwise defined, the term “patient” means an animal, including but not limited to an animal such as a human, monkey, cow, horse, sheep, pig, chicken, turkey, quail, cat, dog, mouse, rat, rabbit, or guinea pig. In one embodiment, the patient is a mammal and in another embodiment the patient is a human. In certain embodiments, the patient can be an adult male or female. In some embodiments, the patient is a male of age about 30 years to about 85 years. In other embodiments, the patient is a female of age about 30 years to about 85 years. In a particular embodiment, the patient has or is susceptible to having (*e.g.*, through genetic or environmental factors) cancer. In a further embodiment, the patient has or is susceptible to having (*e.g.*, through genetic or environmental factors) a tumor. In other embodiments, the patient can be castrated or non-castrated.

[0024] The term “ 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor” as used herein refers to an inhibitor of 17α -hydroxylase/ $C_{17,20}$ -lyase, (which is an enzyme in testosterone synthesis), an analog thereof, derivative thereof, metabolite thereof or pharmaceutically acceptable salt thereof. Also, unless otherwise noted, reference to a particular 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor can include analogs, derivatives, metabolites or pharmaceutically acceptable salts of such particular 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor.

[0025] The term “anti-cancer agent” as used herein refers to any therapeutic agent that directly or indirectly kills cancer cells or directly or indirectly prohibits stops or reduces the proliferation of cancer cells. It should be noted that even though throughout this specification and in the claims the phrase “anti-cancer agent” is written as a singular noun, for example; “an anti-cancer agent” or “the anti-cancer agent,” the phrase “anti-cancer agent” should not be interpreted as being limited to the inclusion of a single anti-cancer agent.

[0026] As used herein, and unless otherwise defined, the phrase “therapeutically effective amount” when used in connection with a 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor or therapeutic agent means an amount of the 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor or therapeutic agent effective for treating a disease or disorder disclosed herein, such as cancer.

[0027] As used herein and unless otherwise defined the phrase “refractory cancer,” means cancer that is not responding to an anti-cancer treatment or cancer that is not

responding sufficiently to an anti-cancer treatment. Refractory cancer can also include recurring or relapsing cancer.

[0028] As used herein and unless otherwise defined the phrase “refractory patient,” means a patient who has refractory cancer.

[0029] As used herein and unless otherwise defined the phrase “relapse cancer,” means cancer that was at one time responsive to an anti-cancer treatment but has become no longer responsive to such treatment or is no longer responding sufficiently to such treatment.

[0030] As used herein and unless otherwise defined the phrase “recurring cancer,” means cancer that has returned after a patient has been earlier diagnosed with cancer, under gone treatment or had been previously diagnosed as cancer-free.

[0031] As used herein and unless otherwise defined the term “derivative” refers to a chemically modified compound wherein the chemical modification takes place at one or more functional groups of the compound. The derivative may retain or improve the pharmacological activity of the compound from which it is derived.

[0032] As used herein and unless otherwise defined the term “analog” refers to a chemical compound that is structurally similar to another but differs slightly in composition (as in the replacement of one atom by an atom of a different element or in the presence of a particular functional group).

[0033] As used herein and unless otherwise defined the phrase “pharmaceutically acceptable salt” refers to any salt of a 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor which retains the biological effectiveness of the 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor. Examples of pharmaceutically acceptable salts include, but are not limited to, acetates, sulfates, pyrosulfates, bisulfates, sulfites, bisulfites, phosphates, monohydrogenphosphates, dihydrogenphosphates, metaphosphates, pyrophosphates, chlorides, bromides, iodides, acetates, propionates, decanoates, caprylates, acrylates, formates, isobutyrate, caproates, heptanoates, propiolates, oxalates, malonates, succinates, suberates, sebacates, fumarates, maleates, butyne-1,4-dioates, hexyne-1,6-dioates, benzoates, chlorobenzoates, methylbenzoates, dinitrobenzoates, hydroxybenzoates, methoxybenzoates, phthalates, sulfonates, xylenesulfonates, phylacetates, phenylpropionates, phenylbutyrates, citrates, lactates, gamma-hydroxybutyrates, glycollates, tartarates, alkanesulfonates (*e.g.* methane-sulfonate or mesylate), propanesulfonates, naphthalene-1-sulfonates, naphthalene-2-

sulfonates, and mandelates. Several of the officially approved salts are listed in Remington: The Science and Practice of Pharmacy, Mack Publ. Co., Easton.

DETAILED DESCRIPTION OF THE INVENTION

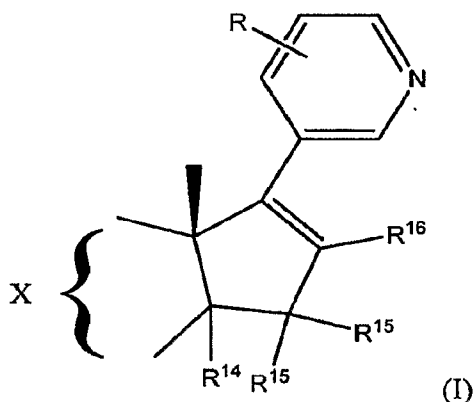
[0034] The methods described herein for treating cancer comprise administering to a mammal, preferably a human, a 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor in addition to at least one therapeutic agent, such as an anti-cancer agent or steroid, particularly a glucocorticoid. The compositions described herein comprise a 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor and at least one additional therapeutic agent, such as an anti-cancer agent or steroid, particularly a corticosteroid or glucocorticoid. Other anti-cancer treatments such as, administration of yet another anti-cancer agent, radiotherapy, chemotherapy, photodynamic therapy, surgery or other immunotherapy, can be used with the methods and compositions.

17α -hydroxylase/ $C_{17,20}$ -lyase Inhibitors

[0035] 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitors have been shown to be useful in the treatment of cancer, specifically hormone-dependent disorders such as, androgen-dependent and estrogen-dependent disorders like prostate cancer and breast cancer respectively, as described in United States Patent No. 5,604,213 to Barrie *et al.*, which is herein incorporated by reference in its entirety.

[0036] In certain embodiments, the 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor can be 17-(3-pyridyl)androsta-5,16-dien-3 β -ol; 17-(3-pyridyl)androsta-3,5,16-triene; 17-(3-pyridyl)androsta-4,16-dien-3-one; 17-(3-pyridyl)estra-1,3,5[10],16-tetraen-3-ol; 17-(3-pyridyl)-5 α -androst-16-en-3 α -ol; 17-(3-pyridyl)-5 α -androst-16-en-3-one; 17-(3-pyridyl)-androsta-4,16-diene-3,11-dione; 17-(3-pyridyl)-androsta-3,5,16-trien-3-ol; 6 α - and 6 β -fluoro-17-(3-pyridyl)androsta-4,16-dien-3-one; 17-(3-pyridyl)androsta-4,16-dien-3,6-dione; 3 α -trifluoromethyl-17-(3-pyridyl)androst-16-en-3 β -ol or their acid addition salts and 3-esters as well as metabolites, analogs, derivatives or a pharmaceutically acceptable salt thereof.

[0037] In certain embodiments, the 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor can have the structure of formula (I):



wherein X represents the residue of the A, B and C rings of a steroid which can be, without limitation, androstan-3 α - or 3 β -ol; androst-5-en-3 α - or 3 β -ol; androst-4-en-3-one; androst-2-ene; androst-4-ene; androst-5-ene; androsta-5,7-dien-3 α or 3 β -ol; androsta-1,4-dien-3-one; androsta-3,5-diene; androsta-3,5-diene-3-ol; estra-1,3,5[10]-triene; estra-1,3,5[10]-trien-3-ol; 5 α -androstan-3-one; androst-4-ene-3,11-dione; 6-fluoroandrost-4-ene-3-one; or androstan-4-ene-3,6-dione; each of which, where structurally permissible, can be further derivatized in one or more of the following ways, including, but not limited to, to form 3-esters; to have one or more carbon or carbon ring double bonds in any of the 5,6-, 6,7-, 7,8-, 9,11- and 11,12-positions; as 3-oximes; as 3-methylenes; as 3-carboxylates; as 3-nitriles; as 3-nitros; as 3-desoxy derivatives; to have one or more hydroxy, halo, C₁₋₄-alkyl, trifluoromethyl, C₁₋₄-alkoxy, C₁₋₄-alkanoyloxy, benzoyloxy, oxo, methylene or alkenyl substituents in the A, B, or C-ring; or to be 19-nor;

R represents a hydrogen atom or an alkyl group of 1-4 carbon atoms;

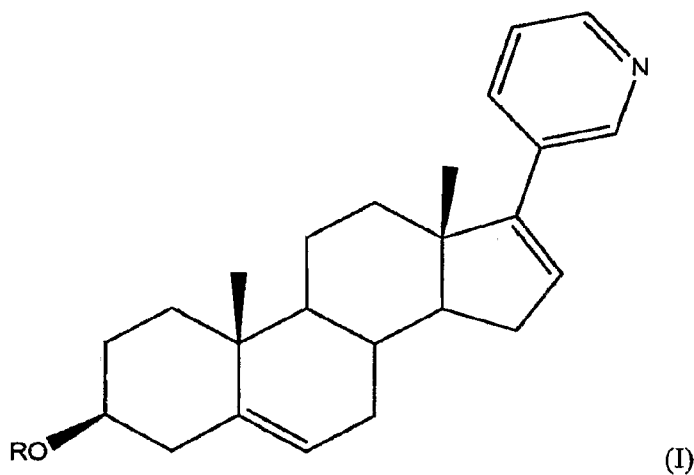
R¹⁴ represents a hydrogen atom, a halogen atom or an alkyl group of 1 to 4 carbon atoms;

each of the R¹⁵ substituents independently represents a hydrogen atom or an alkyl or alkoxy group of 1-4 carbon atoms, a hydroxy group or an alkylcarbonyloxy group of 2 to 5 carbon atoms or together represent an oxo or methylene group or R¹⁴ and one of the R¹⁵ groups together represent a double bond and the other R¹⁵ group represents a hydrogen atom or an alkyl group of 1 to 4 carbon atoms; and

R¹⁶ represents a hydrogen atom, halogen atom, or an alkyl group of 1 to 4 carbon atoms, in the form of the free bases or pharmaceutically acceptable acid addition salts, but excluding 3 β -acetoxy-17-(3-pyridyl)androsta-5,14,16-triene, 3 β ,15 α - and 3 β ,15 β -diacetoxy-17-(3-pyridyl)androsta-5,16-diene and 3 β -methoxy-17-(3-pyridyl)-5 α -androst-16-ene.

Suitable inhibitors also include metabolites, derivatives, analogs, or pharmaceutically acceptable salts of formula (I).

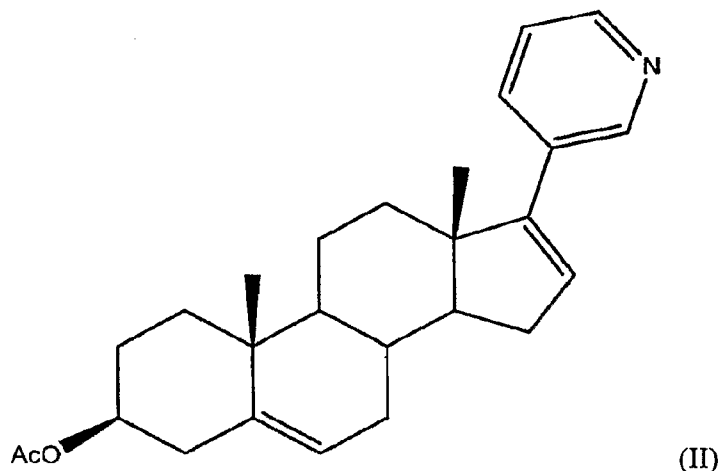
[0038] In another embodiment, the 17 α -hydroxylase/C_{17,20}-lyase inhibitor can have the structure of formula (I):



wherein R represents hydrogen or a lower acyl group having 1 to 4 carbons. Suitable inhibitors also include derivatives, analogs, or pharmaceutically acceptable salts of formula (I).

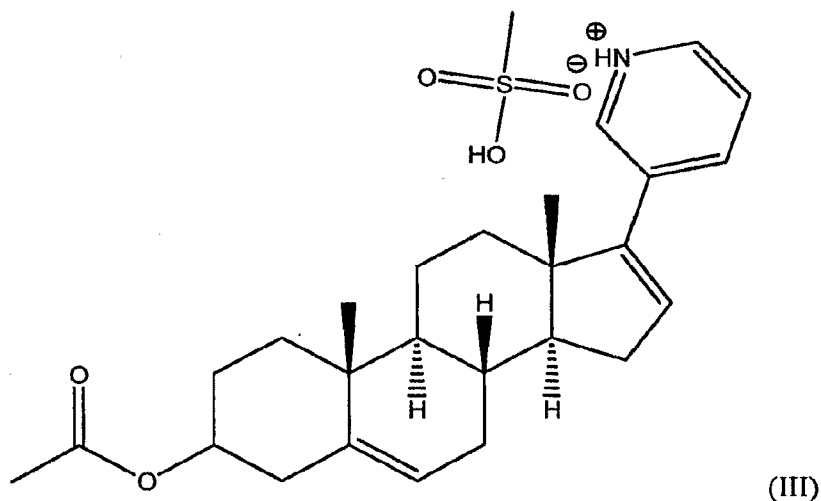
[0039] In still another embodiment, the 17 α -hydroxylase/C_{17,20}-lyase inhibitor can be a 3 β -alkanoyloxy-17-(3-pyridyl) androsta-5,16-diene in which the alkanoyloxy group has from 2 to 4 carbon atoms.

[0040] In a preferred embodiment, the 17 α -hydroxylase/C_{17,20}-lyase inhibitor comprises abiraterone acetate or 3 β -acetoxy-17-(3-pyridyl)androsta-5,16-diene which has the following structural formula:



and pharmaceutically acceptable salts thereof.

[0041] Preferred salts of abiraterone acetate and methods of making such salts are also disclosed in United States Provisional Application No. 60/603,559 to Hunt, which is incorporated by reference in its entirety. Preferred salts include, but are not limited to, acetates, citrates, lactates, alkanesulfonates (e.g. methane-sulfonate or mesylate) and tartarates. Of special interest is the abiraterone acetate mesylate salt (*i.e.* 3 β -acetoxy-17-(3-pyridyl)androsta-5,16-diene mesylate salt) which has the following structural formula:



[0042] The 17 α -hydroxylase/C_{17,20}-lyase inhibitors can be made according to any method known to one skilled in the art. For example, such inhibitors can be synthesized according to the method disclosed in United States Patent Nos. 5,604,213 and 5,618,807 to Barrie *et al.*, herein incorporated by reference. Another method of making 17 α -

hydroxylase/C_{17,20}-lyase inhibitors is disclosed in United States provisional application 60/603,558 to Bury, herein incorporated by reference.

[0043] The amount of 17 α -hydroxylase/C_{17,20}-lyase inhibitor administered to a mammal having cancer is an amount that is sufficient to treat the cancer, whether the 17 α -hydroxylase/C_{17,20}-lyase inhibitor is administered alone or in combination with an additional anti-cancer treatment, such as an additional anti-cancer agent.

Additional Therapeutic Agents

[0044] Suitable compounds that can be used in addition to 17 α -hydroxylase/C_{17,20}-lyase inhibitors as an anti-cancer agent include, but are not limited to, hormone ablation agents, anti-androgen agents, differentiating agents, anti-neoplastic agents, kinase inhibitors, anti-metabolite agents, alkylating agents, antibiotic agents, immunological agents, interferon-type agents, intercalating agents, growth factor inhibitors, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, mitotic inhibitors, matrix metalloprotease inhibitors, genetic therapeutics, and anti-androgens. The amount of the additional anti-cancer agent administered to a mammal having cancer is an amount that is sufficient to treat the cancer whether administered alone or in combination with a 17 α -hydroxylase/C_{17,20}-lyase inhibitor. Below are lists of examples of some of the above classes of anti-cancer agents. The examples are not all inclusive and are for purposes of illustration and not for purposes of limitation. Many of the examples below could be listed in multiple classes of anti-cancer agents and are not restricted in any way to the class in which they are listed in.

[0045] Suitable hormonal ablation agents include, but are not limited to, androgen ablation agents and estrogen ablation agents. In preferred embodiments, the 17 α -hydroxylase/C_{17,20}-lyase inhibitor is administered with a hormonal ablation agent, such as deslorelin, leuprolide, goserelin or triptorelin. Even though throughout this specification and in the claims the phrase "hormonal ablation agent" is written as a singular noun, for example; "a hormonal ablation agent" or "the hormonal ablation agent," the phrase "hormonal ablation agent" should not be interpreted as being limited to the inclusion of a single hormonal ablation agent. The amount of the hormonal ablation agent administered to a mammal having cancer is an amount that is sufficient to treat the cancer whether administered alone or in combination with a 17 α -hydroxylase/C_{17,20}-lyase inhibitor.

[0046] Suitable anti-androgen agents include but are not limited to bicalutamide, flutamide and nilutamide. The amount of the anti-androgen agent administered to a mammal having cancer is an amount that is sufficient to treat the cancer whether administered alone or in combination with a 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor.

[0047] In another embodiment, the 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor may be administered with a differentiating agent. Suitable differentiating agents include, but are not limited to, polyamine inhibitors; vitamin D and its analogs, such as, calcitriol, doxercalciferol and seocalcitol; metabolites of vitamin A, such as, ATRA, retinoic acid, retinoids; short-chain fatty acids; phenylbutyrate; and nonsteroidal anti-inflammatory agents. The amount of the differentiating agent administered to a mammal having cancer is an amount that is sufficient to treat the cancer whether administered alone or in combination with a 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor.

[0048] In another preferred embodiment, the 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor may be administered with an anti-neoplastic agent, including, but not limited to, tubulin interacting agents, topoisomerase inhibitors and agents, acitretin, alstonine, amonafide, amphethinile, amsacrine, ankinomycin, anti-neoplaston, aphidicolin glycinate, asparaginase, baccharin, batracylin, benfluron, benzotript, bromofosfamide, caracemide, carmethizole hydrochloride, chlorsulfaquinoxalone, clanfenur, claviridenone, crisnatol, curaderm, cytarabine, cytoscytin, dacarbazine, datelliptinium, dihaematoporphyrin ether, dihydrolenperone, dinaline, distamycin, docetaxel, elliprabine, elliptinium acetate, epothilones, ergotamine, etoposide, etretinate, fenretinide, gallium nitrate, genkwadaphnin, hexadecylphosphocholine, homoharringtonine, hydroxyurea, ilmofofosine, isoglutamine, isotretinoin, leukoregulin, lonidamine, merbarone, merocyanine derivatives, methylanilinoacridine, minactivin, mitonafide, mitoxantrone, mopidamol, motretinide, N-(retinoyl)amino acids, N-acylated-dehydroalanines, nafazatrom, nocodazole derivative, ocreotide, oquizanocine, paclitaxel, pancratistatin, pazelliptine, piroxantrone, polyhaematoporphyrin, polypreic acid, probimane, procarbazine, proglumide, razoxane, retelliptine, spatol, spirocyclopropane derivatives, spirogermanium, strypoldinone, superoxide dismutase, teniposide, thaliblastine, tocotrienol, topotecan, ukrain, vinblastine sulfate, vincristine, vindesine, vinestramide, vinorelbine, vintriptol, vinzolidine, and withanolides. The amount of the anti-neoplastic agent administered to a mammal having cancer is an amount that is sufficient to treat the cancer whether administered alone or in combination with a 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor.

[0049] The 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitors may also be used with a kinase inhibitor including p38 inhibitors and CDK inhibitors, TNF inhibitors, metallomatrix proteases inhibitors (MMP), COX-2 inhibitors including celecoxib, rofecoxib, parecoxib, valdecoxib, and etoricoxib, SOD mimics or $\alpha_v\beta_3$ inhibitors. The amount of the kinase inhibitor administered to a mammal having cancer is an amount that is sufficient to treat the cancer whether administered alone or in combination with a 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor.

[0050] In another embodiment, the 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor may be administered with an anti-metabolite agent. Suitable anti-metabolite agents may be selected from, but not limited to, 5-FU-fibrinogen, acanthifolic acid, aminothiadiazole, brequinar sodium, carmofur, cyclopentyl cytosine, cytarabine phosphate stearate, cytarabine conjugates, dezaguanine, dideoxycytidine, dideoxyguanosine, didox, doxifluridine, fazarabine, floxuridine, fludarabine phosphate, 5-fluorouracil, N-(2'-furanidyl)-5-fluorouracil, isopropyl pyrrolizine, methobenzaprim, methotrexate, norspermidine, pentostatin, piritrexim, plicamycin, thioguanine, tiazofurin, trimetrexate, tyrosine kinase inhibitors, and uricytin. The amount of the anti-metabolite agent administered to a mammal having cancer is an amount that is sufficient to treat the cancer whether administered alone or in combination with a 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor.

[0051] In another embodiment, the 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor may be administered with an alkylating agent. Suitable alkylating agents may be selected from, but not limited to, aldo-phosphamide analogues, altretamine, anaxirone, bestrabucil, budotitane, carboplatin, carmustine, chlorambucil, cisplatin, cyclophosphamide, cyplatate, diphenylspiromustine, diplatinum cytostatic, elmustine, estramustine phosphate sodium, fotemustine, hepsul-fam, ifosfamide, iproplatin, lomustine, mafosfamide, mitolactol, oxaliplatin, prednimustine, ranimustine, semustine, spiromustine, tauromustine, temozolomide, teroxirone, tetraplatin and trimelamol. The amount of the alkylating agent administered to a mammal having cancer is an amount that is sufficient to treat the cancer, whether administered alone or in combination with a 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor.

[0052] In another preferred embodiment, the 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor may be administered with an antibiotic agent. Suitable antibiotic agents may be selected from, but not limited to, aclarubicin, actinomycin D, actinoplanone, adriamycin, aeroplysinin derivative, amrubicin, anthracycline, azino-mycin-A, bisucaberin, bleomycin

sulfate, bryostatin-1, calicheamicin, chromoximycin, dactinomycin, daunorubicin, ditrissarubicin B, dexamethasone, doxorubicin, doxorubicin-fibrinogen, elsamycin-A, epirubicin, erbstatin, esorubicin, esperamicin-A1, esperamicin-Alb, fostriecin, glidobactin, gregatin-A, grincamycin, herbimycin, corticosteroids such as hydrocortisone, idarubicin, illudins, kazusamycin, kesarirhodins, menogaril, mitomycin, neoenactin, oxalysine, oxaunomycin, peplomycin, pilatin, pirarubicin, porothramycin, prednisone, prednisolone, pyrimidanylin A, rapamycin, rhizoxin, rodorubicin, sibanomicin, siwenmycin, sorangicin-A, sparsomycin, talisomycin, terpenecin, thiazine, tricrozarin A, and zorubicin. The amount of the antibiotic agent administered to a mammal having cancer is an amount that is sufficient to treat the cancer whether administered alone or in combination with a 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor.

[0053] Alternatively, the 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitors may also be used with other anti-cancer agents, including but not limited to, acemannan, aclarubicin, aldesleukin, alemtuzumab, alitretinoin, altretamine, amifostine, amsacrine, anagrelide, anastrozole, aneastim, bexarotene, broxuridine, capecitabine, celmoleukin, cetorelix, cladribine, clotrimazole, daclizumab, dexrazoxane, dilazep, docosanol, doxifluridine, bromocriptine, carmustine, cytarabine, diclofenac, edelfosine, edrecolomab, eflornithine, emitefur, exemestane, exisulind, fadrozole, filgrastim, finasteride, fludarabine phosphate, formestane, fotemustine, gallium nitrate, gemcitabine, glycopine, heptaplatin, ibandronic acid, imiquimod, iobenguane, irinotecan, irsogladine, lanreotide, leflunomide, lenograstim, lentinan sulfate, letrozole, liarozole, lobaplatin, lonidamine, masoprocol, melarsoprol, metoclopramide, mifepristone, miltefosine, mirimostim, mitoguazone, mitolactol, molgramostim, nafarelin, nartograstim, nedaplatin, nilutamide, noscapine, oprelvekin, osaterone, oxaliplatin, pamidronic acid, pegaspargase, pentosan polysulfate sodium, pentostatin, picibanil, pirarubicin, porfimer sodium, raloxifene, raltitrexed, rasburicase, rituximab, romurtide, sargramostim, sizofiran, sobuzoxane, sonermin, suramin, tasonermin, tazarotene, tegafur, temoporfin, temozolomide, teniposide, tetrachlorodecaoxide, thalidomide, thymalfasin, thyrotropin alfa, topotecan, toremifene, trastuzumab, treosulfan, tretinoin, trilostane, trimetrexate, ubenimex, valrubicin, verteporfin, vinorelbine. The amount of the anti-cancer agent administered to a mammal having cancer is an amount that is sufficient to treat the cancer whether administered alone or in combination with a 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor.

[0054] The 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitors may also be administered or combined with steroids, such as corticosteroids or glucocorticoids. The 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitors and the steroid may be administered in the same or in different compositions. Non-limiting examples of suitable steroids include hydrocortisone, prednisone, or dexamethasone. The amount of the steroid administered to a mammal having cancer is an amount that is sufficient to treat the cancer whether administered alone or in combination with a 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor.

[0055] In one embodiment, provided herein are methods and compositions comprising both abiraterone acetate and a steroid particularly a corticosteroid, or more particularly a glucocorticoid. Steroids within the scope of the disclosure include, but are not limited to, (1) hydrocortisone (cortisol; cypionate (*e.g.*, CORTEF), oral; sodium phosphate injection (HYDROCORTONE PHOSPHATE); sodium succinate (*e.g.*, A-HYDROCORT, Solu-CORTEF); cortisone acetate oral or injection forms, etc.), (2) dexamethasone (*e.g.*, Decadron, oral; Decadron-LA injection, etc.), (3) prednisolone (*e.g.*, Delta-CORTEF, prednisolone acetate (ECONOPRED), prednisolone sodium phosphate (HYDELTRASOL), prednisolone tebutate (HYDELTRA-TBA, etc.)), or (4) prednisone (*e.g.*, DELTASONE, etc.) and combinations thereof. See, *e.g.*, GOODMAN & GILMAN'S THE PHARMACOLOGICAL BASIS OF THERAPEUTICS, 10TH EDITION 2001.

[0056] In a specific embodiment, single unit solid oral dosage forms which comprise an amount from about 50 mg to about 300 mg of abiraterone acetate and an amount from about 0.5 mg to about 3.0 mg of a steroid, *e.g.*, glucocorticoid in a single composition, optionally with excipients, carriers, diluents, etc. is contemplated. For instance, the single unit dosage form can comprise about 250 mg of abiraterone acetate and about 1.0 mg, 1.25 mg, 1.5 mg, or 2.0 mg of a steroid, such as but not limited to corticosteroids or glucocorticoids.

Administration of the 17α -hydroxylase/ $C_{17,20}$ -lyase Inhibitor and an Additional Therapeutic Agent

[0057] The 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor and the additional therapeutic agent, such as an anti-cancer agent or a steroid can be administered by any method known to one skilled in the art. In certain embodiments, the 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor and the additional therapeutic agent can be in separate compositions prior to administration.

In the alternative, the 17 α -hydroxylase/C_{17,20}-lyase inhibitor and the additional therapeutic agent can be combined into a single composition for administration.

[0058] The 17 α -hydroxylase/C_{17,20}-lyase inhibitor and the additional therapeutic agent can be administered sequentially or simultaneously. If administered sequentially, the order of administration is flexible. For instance, 17 α -hydroxylase/C_{17,20}-lyase inhibitor acetate can be administered prior to administration of the additional therapeutic agent. Alternatively, administration of the additional therapeutic agent can precede administration of 17 α -hydroxylase/C_{17,20}-lyase inhibitor.

[0059] Whether they are administered as separate compositions or in one composition, each composition is preferably pharmaceutically suitable for administration. Moreover, the 17 α -hydroxylase/C_{17,20}-lyase inhibitor and the therapeutic agent, if administered separately, can be administered by the same or different modes of administration. Examples of modes of administration include parenteral (*e.g.*, subcutaneous, intramuscular, intraorbital, intracapsular, intraspinal, intrasternal, intravenous, intradermal, intraperitoneal, intraportal, intra-arterial, intrathecal, transmucosal, intra-articular, and intrapleural,), transdermal (*e.g.*, topical), epidural, and mucosal (*e.g.*, intranasal) injection or infusion, as well as oral, inhalation, pulmonary, and rectal administration. In specific embodiments, both are oral.

[0060] For example, the 17 α -hydroxylase/C_{17,20}-lyase inhibitor can be administered transdermally and the additional therapeutic agent can be administered parenterally. Alternatively, the 17 α -hydroxylase/C_{17,20}-lyase inhibitor can be administered orally, such as in a tablet, caplet or capsule, while the additional therapeutic agent can be administered intravenously. Such intravenously administered therapeutic agents include, but are not limited to, docetaxel injections, such as Taxotere[®]; paclitaxel injections, such as Paclitaxel[®] and mitoxantrone injections, such as Novantrone[®]. Also, the additional therapeutic agent can be in the form of depots or implants such as leuprolide depots and implants, *e.g.* Viadur[®] and Lupron Depot[®]; triptorelin depots, *e.g.* Trelstar[®]; goserelin implants, *e.g.* Zoladex[®].

[0061] The suitable daily dosage of the 17 α -hydroxylase/C_{17,20}-lyase inhibitor depends upon a number of factors, including, the nature of the severity of the condition to be treated, the particular inhibitor, the route of administration and the age, weight, and response of the individual patient. Suitable daily dosages of 17 α -hydroxylase/C_{17,20}-lyase inhibitors can generally range from about 0.0001 mg/kg/day to about 1000 mg/kg/day, or

from about 0.001 mg/kg/day to about 200 mg/kg/day, or from about 0.01 mg/kg/day to about 200 mg/kg/day, or from about 0.01 mg/kg/day to about 100 mg/kg/day in single or multiple doses.

[0062] In some embodiments, the 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor can be administered in an amount from about 0.004 mg/day to about 5,000 mg/day, or from about 0.04 mg/day to about 3,000 mg/day, or from about 0.4 mg/day to about 1500 mg/day. In certain embodiments, the 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor can be administered in an amount from about 0.1 mg/day to about 2000 mg/day or from about 1 mg/day to about 2000 mg/day or from about 50 mg/day to about 2000 mg/day or from about 100 mg/day to about 1500 mg/day or from about 5 mg/day to about 1,000 mg/day or from about 5 mg/day to about 900 mg/day or from about 10 mg/day to about 800 mg/day or from about 15 mg/day to about 700 mg/day or from about 20 mg/day to about 600 mg/day or from about 25 mg/day to about 500 mg/day in single or multiple doses.

[0063] In certain embodiments, the 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor is co-administered with an additional anti-cancer agent such as mitoxantrone, paclitaxel or docetaxel. For example, a method for the treatment of a cancer in a mammal comprises administering an amount of abiraterone acetate and an amount of mitoxantrone. For example, the abiraterone acetate can be administered in an amount of about 0.01 mg/kg/day to about 100 mg/kg/day and the mitoxantrone can be administered in an amount of about 0.1 mg/m² to about 20 mg/m². Preferably, the mitoxantrone is administered over a period of between about 10 to about 20 minutes once every 21 days.

[0064] Also, a method for the treatment of a cancer in a mammal can comprise administering an amount of abiraterone acetate and an amount of paclitaxel. In one embodiment, the abiraterone acetate can be administered in an amount of about 0.01 mg/kg/day to about 100 mg/kg/day and the paclitaxel can be administered in the amount of about 1 mg/m² to about 175 mg/m². Preferably, the paclitaxel is administered over a period of between about 2 to about 5 hours once every three months.

[0065] Additionally, a method for the treatment of a cancer in a mammal comprises administering an amount of abiraterone acetate and an amount of docetaxel. For example, the abiraterone acetate can be administered in an amount of about 0.01 mg/kg/day to about 100 mg/kg/day and the docetaxel can be administered in an amount of about 1 mg/m² to about 100 mg/m². Preferably, the docetaxel is administered over a period of between about 1 to about 2 hours once every three weeks.

[0066] In certain embodiments, the 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor is administered along with an anti-cancer agent that comprises a hormonal ablation agent, including, but not limited to, leuprolide, goserelin, or triptorelin. For example, one method for the treatment of a cancer in a mammal also comprises administering an amount of abiraterone acetate and an amount of leuprolide. The amount of abiraterone acetate can be about 0.01 mg/kg/day to about 100 mg/kg/day and the amount of leuprolide can be about 0.01 mg to about 200 mg over a period of about 3 days to about 12 months. Preferably, the leuprolide is administered in the amount of about 3.6 mg of leuprolide over a period of about 3 days to about 12 months.

[0067] Additionally, the methods for the treatment of cancer in a mammal include administering an amount of abiraterone acetate and an amount of goserelin. For example, the amount of abiraterone acetate can be about 0.01 mg/kg/day to about 100 mg/kg/day and the amount of goserelin can be about 0.01 mg to about 20 mg over a period of about 28 days to about 3 months. Preferably, the goserelin is administered in the amount of about 3.6 mg to about 10.8 mg over a period of about 28 days to about 3 months.

[0068] In certain embodiments the methods for the treatment of cancer in a mammal comprises administering an amount of abiraterone acetate and an amount of triptorelin. For example, the amount of abiraterone acetate can be about 0.01 mg/kg/day to about 100 mg/kg/day and the amount of triptorelin can be about 0.01 mg to about 20 mg, over a period of about 1 month, preferably the triptorelin is administered in the amount of about 3.75 mg over a period of about 1 month.

[0069] Also, in one embodiment, the method for the treatment of a cancer in a mammal comprises administering an amount of abiraterone acetate and an amount of seocalcitol. For instance, the method involves administering an amount of about 0.01 mg/kg/day to about 100 mg/kg/day of abiraterone acetate and an amount of about 0.1 μ g/day to about 500 μ g/day of seocalcitol, such as about 100 μ g/day of seocalcitol.

[0070] In another embodiment, the method for the treatment of a cancer in a mammal comprises administering an amount of abiraterone acetate and an amount of bicalutamide. For instance, the method involves administering an amount of about 0.01 mg/kg/day to about 100 mg/kg/day of abiraterone acetate and an amount of about 1 mg/day to about 300 mg/day of bicalutamide.

[0071] In yet another embodiment, the method for the treatment of a cancer in a mammal comprises administering an amount of abiraterone acetate and an amount of

flutamide. For example, the method comprises administering an amount of about 0.01 mg/kg/day to about 100 mg/kg/day of abiraterone acetate and an amount of about 1 mg/day to about 2000 mg/day of flutamide.

[0072] Moreover, the method for the treatment of a cancer in a mammal can comprise administering an amount of a 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor such as abiraterone acetate and an amount of a glucocorticoid including, but not limited to, hydrocortisone, prednisone or dexamethasone. For example, the method can comprise administering an amount of about 50 mg/day to about 2000 mg/day of abiraterone acetate and an amount of about 0.01 mg/day to about 500 mg/day of hydrocortisone. In other instances, the method can comprise administering an amount of about 500 mg/day to about 1500 mg/day of abiraterone acetate and an amount of about 10 mg/day to about 250 mg/day of hydrocortisone.

[0073] The method for the treatment of a cancer can also comprise administering an amount of a 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor, such as abiraterone acetate, and an amount of a glucocorticoid, such as prednisone. For example, the method can comprise administering an amount of about 50 mg/day to about 2000 mg/day of abiraterone acetate and an amount of about 0.01 mg/day to about 500 mg/day of prednisone. Also, the method can comprise administering an amount of about 500 mg/day to about 1500 mg/day of abiraterone acetate and an amount of about 10 mg/day to about 250 mg/day of prednisone.

[0074] In addition, the method for the treatment of a cancer can also comprise administering an amount of a 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor, such as abiraterone acetate, and an amount of a glucocorticoid, such as dexamethasone. For example, the method can comprise administering an amount of about 50 mg/day to about 2000 mg/day of abiraterone acetate and an amount of about 0.01 mg/day to about 500 mg/day of dexamethasone. Also, the method can comprise administering an amount of about 500 mg/day to about 1500 mg/day of abiraterone acetate and an amount of about 0.5 mg/day to about 25 mg/day of dexamethasone.

Compositions Containing a 17α -hydroxylase/ $C_{17,20}$ -lyase Inhibitor and an Additional Therapeutic Agent

[0075] In certain embodiments, the compositions can contain a combination of a 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor, preferably abiraterone acetate, and any of the therapeutic agents recited above. Whether the 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor and

the additional therapeutic agent are administered in separate compositions or as a single composition, the compositions can take various forms. For example, the compositions can take the form of solutions, suspensions, emulsions, tablets, pills, capsules, powders or sustained-release formulations, depending on the intended route of administration.

[0076] For topical or transdermal administration, the compositions can be formulated as solutions, gels, ointments, creams, suspensions or salves.

[0077] For oral administration, the compositions may be formulated as tablets, pills, dragees, troches, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient to be treated.

[0078] The composition may also be formulated in rectal or vaginal compositions such as suppositories or retention enemas that contain conventional suppository bases such as cocoa butter or other glycerides.

[0079] In addition to the formulations described previously, the composition may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the therapeutic agents may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

[0080] Additionally, the composition may be delivered using a sustained-release system, such as semi-permeable matrices of solid polymers containing the composition. Various forms of sustained-release materials have been established and are well known by those skilled in the art. Sustained-release capsules may, depending on their chemical nature can release the composition over a period of hours, days, weeks, months. For example a sustained release capsule can release the compositions over a period of 100 days or longer. Depending on the chemical nature and the biological stability of the composition, additional strategies for stabilization may be employed.

[0081] The compositions can further comprise a pharmaceutically acceptable carrier. The term "carrier" refers to a diluent, adjuvant (*e.g.*, Freund's adjuvant (complete and incomplete)), excipient, or vehicle with which the therapeutic is administered.

[0082] For parenteral administrations, the composition can comprise one or more of the following carriers: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerin, propylene glycol or other synthetic solvents; antibacterial

agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. The parenteral preparation can be enclosed in ampules, disposable syringes or multiple dose vials made of glass or plastic.

[0083] For oral solid formulations suitable carriers include fillers such as sugars, e.g., lactose, sucrose, mannitol and sorbitol; cellulose preparations such as maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, fats and oils; granulating agents; and binding agents such as microcrystalline cellulose, gum tragacanth or gelatin; disintegrating agents, such as cross-linked polyvinylpyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate, Primogel, or corn starch; lubricants, such as magnesium stearate or Sterotes; glidants, such as colloidal silicon dioxide; a sweetening agent, such as sucrose or saccharin; or flavoring agents, such as peppermint, methyl salicylate, or orange flavoring. If desired, solid dosage forms may be sugar-coated or enteric-coated using standard techniques.

[0084] For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, phosphate buffered saline (PBS). In all cases, the composition must be sterile and should be fluid to the extent that easy injectability with a syringe. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars; polyalcohols such as mannitol, sorbitol; sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

[0085] Also for intravenous administration, the compositions may be formulated in solutions, preferably in physiologically compatible buffers such as Hanks's solution, Ringer's solution, or physiological saline buffer. The solution may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. In a preferred embodiment, the compositions are formulated in sterile solutions.

[0086] For transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, detergents, bile salts, and fusidic acid derivatives. Transmucosal administration can be accomplished through the use of nasal sprays or suppositories.

[0087] For administration by inhalation, the compositions may be formulated as an aerosol spray from pressurized packs or a nebulizer, with the use of a suitable propellant, *e.g.*, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of the composition and a suitable powder base such as lactose or starch.

[0088] The pharmaceutical compositions may be manufactured by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or lyophilizing processes.

[0089] One example of a composition comprising a 17 α -hydroxylase/C_{17,20}-lyase inhibitor and an additional therapeutic agent is an oral composition or composition suitable for oral administration comprising abiraterone acetate in combination with a steroid. For example, the oral composition can be a solid dosage form such as a pill, a tablet or a capsule. The oral composition can comprise about 10 mg, 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 250 mg, 300 mg, 350 mg, 400 mg, 450 mg, 500 mg, 550 mg, 600 mg, 650 mg, 700 mg, 750 mg, 800 mg, 850 mg, 900 mg, 950 mg, or 1000 mg of abiraterone acetate. The oral composition can comprises about 0.25 mg, 0.5 mg, 0.75 mg, 1.0 mg, 1.25 mg, 1.5 mg, 1.75 mg, 2.0 mg, 2.25 mg, 2.5 mg, 2.75 mg, 3.0 mg, 3.25 mg, 3.5 mg, 3.75 mg, 4.0 mg, 4.25 mg, 4.5 mg, 4.75 mg, 5.0 mg, 7.5 mg, 10 mg, 20 mg, 30 mg, 40 mg or 50 mg of a steroid, such as a glucocorticoid.

[0090] In one embodiment, the oral composition can comprise about 50 mg to about 500 mg of abiraterone acetate and an amount of about 0.25 mg to about 3.5 mg of the

steroid, such as hydrocortisone, prednisone or dexamethasone. In other instances, the composition can comprise about 50 mg to about 300 mg of abiraterone acetate and an amount of about 1.0 mg to about 2.5 mg of the steroid, such as hydrocortisone, prednisone or dexamethasone. In another embodiment the composition can comprise about 50 mg to about 300 mg of abiraterone acetate and about 0.5 mg to about 3.0 mg of a steroid. For example, the oral composition can be a tablet containing 250 mg of abiraterone acetate; 1.25 mg or 2.0 mg of a steroid, such as hydrocortisone, prednisone or dexamethasone; and one or more carriers, excipients, diluents or additional ingredients. Additionally, the oral composition can be a capsule containing 250mg of abiraterone acetate; 1.25 mg or 2.0 mg of a steroid, such as hydrocortisone, prednisone or dexamethasone; and one or more carriers, excipients, diluents or additional ingredients.

[0091] The description contained herein is for purposes of illustration and not for purposes of limitation. The methods and compositions described herein can comprise any feature described herein either alone or in combination with any other feature(s) described herein. Changes and modifications may be made to the embodiments of the description. Furthermore, obvious changes, modifications or variations will occur to those skilled in the art. Also, all references cited above are incorporated herein, in their entirety for all purposes related to this disclosure.

[0092] Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

[0093] The reference to any prior art in this specification is not and should not be taken as an acknowledgement or any form of suggestion that the prior art forms part of the common general knowledge in Australia.

CLAIMS

1. A use of a therapeutically effective amount of abiraterone acetate or a pharmaceutically acceptable salt thereof in the preparation of a medicament for the treatment of a prostate cancer in a human, wherein the medicament is administered in addition to a therapeutically effective amount of prednisone.
2. The use according to claim 1, wherein the medicament is administered at a dose of about 50 mg/day to about 2000 mg/day of abiraterone acetate or pharmaceutically acceptable salt thereof.
3. The use according to claim 1, wherein the medicament is administered at a dose of about 500 mg/day to about 1500 mg/day of abiraterone acetate or pharmaceutically acceptable salt thereof.
4. The use according to claim 1, wherein the medicament is administered at a dose of about 1000 mg/day of abiraterone acetate or pharmaceutically acceptable salt thereof.
5. The use according to any one of claims 1 to 4, wherein the medicament is administered in at least one oral dosage form comprising about 250 mg of abiraterone acetate or a pharmaceutically acceptable salt thereof.
6. The use according to claim 5, wherein the prednisone is administered at a dose of about 0.01 mg/day to about 500 mg/day.
7. The use according to claim 5, wherein the prednisone is administered at a dose of about 10 mg/day to about 250 mg/day.
8. The use according to any one of claims 1 to 7, wherein the medicament is administered sequentially with the therapeutically effective amount of prednisone.
9. The use according to any one of claims 1 to 7, wherein the medicament is administered simultaneously with the therapeutically effective amount of prednisone.

10. A use of a therapeutically effective amount of abiraterone acetate or a pharmaceutically acceptable salt thereof in the preparation of a medicament for the treatment of a refractory prostate cancer in a human, wherein the medicament is administered in addition to a therapeutically effective amount of prednisone.
11. The use according to claim 10, wherein the refractory prostate cancer is not responding to at least one anti-cancer agent.
12. The use according to any one of claims 1 to 11, wherein said human is currently receiving an anti-cancer agent.
13. The use according to any one of claims 10 to 12, wherein the medicament is administered sequentially with the therapeutically effective amount of prednisone.
14. The use according to any one of claims 10 to 12, wherein the medicament is administered simultaneously with the therapeutically effective amount of prednisone.
15. The use according to any one of claims 1 to 14, wherein the medicament is administered at a dose of about 50 mg/day to about 2000 mg/day abiraterone acetate or pharmaceutically acceptable salt thereof in addition to about 10 mg/day to about 250 mg/day of prednisone.
16. A compound when used in the treatment of a prostate cancer in a human, wherein the compound is a therapeutically effective amount of abiraterone acetate or a pharmaceutically acceptable salt thereof, and wherein the compound is administered in addition to a therapeutically effective amount of prednisone.
17. A compound when used in the treatment of a refractory prostate cancer in a human, wherein the compound is a therapeutically effective amount of abiraterone acetate or a pharmaceutically acceptable salt thereof, and wherein the compound is administered in addition to a therapeutically effective amount of prednisone.

18. The compound when used according to claim 16 or claim 17, wherein the therapeutically effective amount of the abiraterone acetate or pharmaceutically acceptable salt thereof is from about 50 mg/day to about 2000 mg/day.
19. The compound when used according to claim 18, wherein the therapeutically effective amount of the abiraterone acetate or pharmaceutically acceptable salt thereof is from about 500 mg/day to about 1500 mg/day.
20. The compound when used according to claim 19, wherein the therapeutically effective amount of the abiraterone acetate or pharmaceutically acceptable salt thereof is about 1000 mg/day.
21. The compound when used according to any one of claims 16 to 20, wherein the therapeutically effective amount of the abiraterone acetate or a pharmaceutically acceptable salt thereof is administered in at least one oral dosage form comprising about 250 mg of abiraterone acetate or a pharmaceutically acceptable salt thereof.
22. The compound when used according to any one of claims 16 to 21, wherein the therapeutically effective amount of the prednisone is from about 0.01 mg/day to about 500 mg/day.
23. The compound when used according to claim 22, wherein the therapeutically effective amount of the prednisone is from about 10 mg/day to about 250 mg/day.
24. The compound when used according to any one of claims 16 to 23, wherein the therapeutically effective amount of the abiraterone acetate or pharmaceutically acceptable salt thereof is administered sequentially with the therapeutically effective amount of prednisone.
25. The compound when used according to any one of claims 16 to 23, wherein the therapeutically effective amount of the abiraterone acetate or pharmaceutically acceptable salt thereof is administered simultaneously with the therapeutically effective amount of prednisone.
26. The compound when used according to any one of claims 17 to 25, wherein the refractory prostate cancer is not responding to at least one anti-cancer agent.

27. The compound when used according to any one of claims 16 to 26, wherein said human is currently receiving an anti-cancer agent.
28. A method for the treatment of a prostate cancer in a human, comprising administering to said human a therapeutically effective amount of abiraterone acetate or a pharmaceutically acceptable salt thereof in addition to a therapeutically effective amount of prednisone.
29. A method for the treatment of refractory prostate cancer in a human, comprising administering to said human a therapeutically effective amount of abiraterone acetate or a pharmaceutically acceptable salt thereof in addition to a therapeutically effective amount of prednisone.
30. The method according to claim 28 or claim 29, wherein the therapeutically effective amount of the abiraterone acetate or pharmaceutically acceptable salt thereof is from about 50 mg/day to about 2000 mg/day.
31. The method according to claim 30, wherein the therapeutically effective amount of the abiraterone acetate or pharmaceutically acceptable salt thereof is from about 500 mg/day to about 1500 mg/day.
32. The method according to claim 31, wherein the therapeutically effective amount of the abiraterone acetate or pharmaceutically acceptable salt thereof is about 1000 mg/day.
33. The method according to any one of claims 28 to 32, wherein the therapeutically effective amount of the abiraterone acetate or a pharmaceutically acceptable salt thereof is administered in at least one oral dosage form comprising about 250 mg of abiraterone acetate or a pharmaceutically acceptable salt thereof.
34. The method according to any one of claims 28 to 33, wherein the therapeutically effective amount of the prednisone is from about 0.01 mg/day to about 500 mg/day.
35. The method according to claim 34, wherein the therapeutically effective amount of the prednisone is from about 10 mg/day to about 250 mg/day.

36. The method according to any one of claims 28 to 35, wherein the therapeutically effective amount of the abiraterone acetate or pharmaceutically acceptable salt thereof is administered sequentially with the therapeutically effective amount of prednisone.

37. The method according to any one of claims 28 to 35, wherein the therapeutically effective amount of the abiraterone acetate or pharmaceutically acceptable salt thereof is administered simultaneously with the therapeutically effective amount of prednisone.

38. The method according to any one of claims 29 to 37, wherein the refractory prostate cancer is not responding to at least one anti-cancer agent.

39. The method according to any one of claims 28 to 38, wherein said human is currently receiving an anti-cancer agent.

40. The method according to any one of claims 28 to 39, wherein the therapeutically effective amount of abiraterone acetate or pharmaceutically acceptable salt thereof is about 1000 mg/day and the therapeutically effective amount of prednisone is about 10 mg/day, and wherein the abiraterone acetate or pharmaceutically acceptable salt thereof and prednisone are administered in separate dosage forms, preferably wherein the abiraterone acetate is administered in an oral dosage form comprising about 250 mg abiraterone acetate or a pharmaceutically acceptable salt thereof.

41. The method according to claim 40, wherein the refractory prostate cancer has failed to respond to androgen deprivation therapy.

42. The method according to claim 41, wherein the androgen deprivation therapy is castration.

43. The method according to claim 40, wherein the at least one anti-cancer agent is prednisone.

44. The method according to claim 40, wherein the at least one anti-cancer agent is abiraterone acetate.

45. The method according to claim 40, wherein the at least one anti-cancer agent is a taxane.
46. The method according to claim 40, wherein the at least one anti-cancer agent is docetaxel.
47. The method according to claim 40, wherein the refractory prostate cancer is metastatic prostate cancer.
48. Abiraterone acetate when used in the treatment of a prostate cancer in a human, wherein the abiraterone acetate is administered in an amount of about 50 mg/day to about 2000 mg/day, in addition to about 10 mg/day to about 250 mg/day of prednisone.
49. A pharmaceutical composition when used in the treatment of a prostate cancer in a human comprising a therapeutically effective amount of abiraterone acetate or a pharmaceutically acceptable salt thereof and a therapeutically effective amount of prednisone.
50. The composition according to claim 49, wherein the therapeutically effective amount of the abiraterone acetate or pharmaceutically acceptable salt thereof is from about 50 mg to about 500 mg and the therapeutically effective amount of prednisone is from about 0.25 mg to about 3.5 mg.
51. The composition according to claim 49, wherein the composition is suitable for oral administration.
52. The composition according to claim 51, wherein the composition is a solid dosage form.
53. The composition according to claim 52, wherein the composition is in the form of a pill, tablet or capsule.
54. The composition according to claim 49, wherein the prostate cancer is a refractory prostate cancer.

55. The use of a therapeutically effective amount of abiraterone acetate or a pharmaceutically acceptable salt thereof in the preparation of a medicament for the treatment of a prostate cancer in a human according to claim 1, substantially as hereinbefore described.
56. The compound when used in the treatment of a prostate cancer in a human according to claim 16, substantially as hereinbefore described.
57. The use of a therapeutically effective amount of abiraterone acetate or a pharmaceutically acceptable salt thereof in the preparation of a medicament for the treatment of a refractory prostate cancer in a human according to claim 10, substantially as hereinbefore described.
58. The compound when used in the treatment of a refractory prostate cancer in a human according to claim 17, substantially as hereinbefore described.
59. Abiraterone acetate when used in the treatment of a prostate cancer in a human according to claim 48, substantially as hereinbefore described.
60. A pharmaceutical composition when used in the treatment of a prostate cancer in a human according to claim 49, substantially as hereinbefore described.