(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
26 May 2016 (26.05.2016)

WIPO | PCT

(10) International Publication Number
WO 2016/081383 A1

(51) International Patent Classification:
A61K 31/56 (2006.01)

(21) International Application Number:
PCT/US2015/060940

(22) International Filing Date:
16 November 2015 (16.11.2015)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/080,868 17 November 2014 (17.11.2014) US

(71) Applicant: **ARNO THERAPEUTICS, INC.** [US/US]; 200 Route 31 North, Flemington, New Jersey 08822 (US).

(72) Inventors: **ZUKIWSKI, Alexander**; 12003 Tregoning Place, Clarksburg, Maryland 20871 (US). **PRONIUK, Stefan**; 1781 Spyglass Drive #399, Austin, Texas 78746 (US).

(74) Agent: **CUBERT, Jeremy A.**; VLP Law Group LLP, 555 Bryant Street, Suite 820, Palo Alto, California 94301 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, 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, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, 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, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

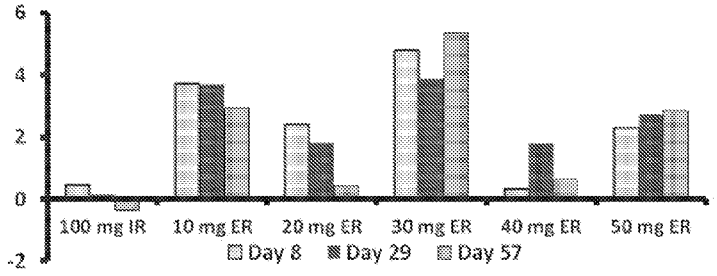
Published:

— *with international search report (Art. 21(3))*

WO 2016/081383 A1

(54) Title: ONAPRISTONE EXTENDED-RELEASE COMPOSITIONS AND METHODS

Figure 3



(57) Abstract: Onapristone extended-release formulations and methods of administering onapristone extended-release formulations are provided. Onapristone extended-release formulations provide sufficient therapeutic activity as compared to immediate-release formulations with reduced potential for adverse side effects. Aspects described herein provide extended-release pharmaceutical compositions comprising onapristone as the active ingredient in an amount from about 2 mg to about 100 mg. The extended-release pharmaceutical compositions (also referred to herein as ER formulations) further comprise excipients suitable for the desired dosage form (e.g., tablet, capsule, etc.) and for delaying the release of the active ingredient.

ONAPRISTONE EXTENDED-RELEASE COMPOSITIONS AND METHODS

PRIORITY CLAIM

[0001] This application claims priority to U.S. Provisional Patent Application Serial No. 62/080,868, filed November 17, 2014. The above referenced application is incorporated herein by reference as if restated in full. The above referenced application and all references cited herein, including but not limited to patents and patent applications, are incorporated by reference in their entirety.

BACKGROUND

[0002] Onapristone (ONA) is an anti-progestin drug and progesterone receptor antagonist which was originally developed for potential contraceptive use and the use in benign gynecological disorders such as the treatment of uterine leiomyomas. However, onapristone has demonstrated substantial activity in advanced breast cancer. It is thought that ONA binds to the progesterone receptor (PR), preventing the PR from binding to DNA and thereby inhibiting or eliminating PR-induced DNA transcription. See, e.g., Klijn et al., Progesterone antagonists and progesterone receptor modulation in the treatment of breast cancer, Steroids, v. 65, pp. 825-830 (2000); Jonat et al., The clinical efficacy of progesterone antagonists in breast cancer, Endocrine Therapy of Breast Cancer, pp. 117-124.

[0003] Onapristone is a type I progesterone receptor (PR) antagonist, which prevents PR-induced DNA transcription. Presence of transcriptionally activated PR (APR) in tissue samples from a cancer patient, measured using, for example, an immunohistochemistry companion diagnostic procedure, indicates susceptibility to treatment with onapristone anticancer activity.. Onapristone anti-cancer activity is documented in multiple pre-clinical models and clinical studies in patients with hormone therapy-naive or tamoxifen-resistant breast cancer. Despite promising activity in breast cancer models, the development of onapristone as an oncology drug was terminated due to liver function test abnormalities. See, e.g., Robertson et al., Eur J Cancer. 35(2):214-8 (Feb. 1999).

[0004] Expression of the progesterone receptor (PR) has been described in breast [Mote 2000, Lange 2008], endometrial [Kim 2013, Mortel 1984], prostate [Lange 2007, Bonkhoff 2001], ovarian [Sieh 2013], and several other cancers [Yin 2010, Ishibashi 2005, Blankenstein 2000]. Antiprogestins have been shown to have an inhibitory effect on the growth of different type of cancer cells, and antiprogestin treatment has been studied in breast [Jonat 2013], endometrial [Thigpen 1999], prostate [Taplin 2008] cancers and uterine sarcomas [Koivisto-Korander 2007].

[0005] The effects of progesterone are mediated by two distinct nuclear receptor proteins, PRA and PRB, two transcriptional isoforms of the single PR gene. In luminal epithelial cells of the normal breast and in normal endometrium, both PR isoforms are expressed and are required to mediate the physiological effects of progestin ligands [Mote 2002, Arnett-Mansfield 2004]. The two PR isoforms have both been detected in malignant tissues, such as breast, endometrial, ovarian and prostate cancers [Cottu 2015].

[0006] ONA is a type I antiprogestin which prevents PR monomers from dimerizing, inhibits ligand-induced phosphorylation, prevents association of the PR with its co-activators, and thus prevents PR-mediated DNA transcription. ONA does not allow the PR complex to bind to DNA, does not or minimally modulates PR-mediated genes, and inhibits ligand-induced PR phosphorylation, in contrast to other antiprogestins [Beck 1996; Afhüppe 2009]. Preclinical activity has been shown in several models, including endometrial cancer [Mueller 2003] and the clinical anticancer activity of ONA has been previously documented in patients with hormone therapy-naive [Robertson 1999] or tamoxifen-resistant [Jonat 2002] breast cancer.

[0007] Transcriptionally activated PR (APR) can be detected by observational evaluation of the subnuclear distribution pattern using immunohistochemistry (IHC). Using this method, APR can be used as a potentially predictive IHC biomarker in endometrioid cancer of the uterus. See, U.S. Patent Number 9,046,534. APR detection is being developed as a companion diagnostic to identify patients more likely to respond to ONA [Bonneterre 2015].

[0008] Early clinical studies employing the original immediate release (IR) formulation of ONA have shown that ONA is well-tolerated with the exception of abnormalities in liver

function tests (LFTs) [Cameron 1996, Cameron 2003, Croxatto 1994, Jonat 2002, Robertson 1999]. Studies with the original IR formulation were discontinued due to these LFT abnormalities. Id.

[0009] Previously, onapristone was provided to patients with cancer (e.g., breast, endometrial, others) in an immediate release formulation of 100 mg and provided QD (once per day). Onapristone has also been given to patients in endocrinology studies, at immediate release doses of 1 and 10 mg doses resulting in a dose-dependent effect of onapristone on suppression of gonadotrophin (luteinizing hormone [LH] and follicle-stimulating hormone [FSH]) secretion. Cameron 2003. However, these studies used immediate release formulations of onapristone of unknown purity. Importantly, these studies addressed the dose and formulation of onapristone suitable for potential contraceptive use rather than the dose and formulation suitable for treating a disease such as cancer.

[0010] What is needed is an improved formulation of onapristone which allow for a continuous suppression of the PR and methods of administering the same resulting in sufficient bioavailability to provide clinical benefit to cancer patients at doses which result in less toxicity than the previous clinical experience with onapristone.

SUMMARY

[0011] Aspects described herein provide extended-release pharmaceutical compositions comprising onapristone as the active ingredient in an amount from about 2 mg to about 100 mg. The extended-release pharmaceutical compositions (also referred to herein as ER formulations) further comprise excipients suitable for the desired dosage form (e.g., tablet, capsule, etc.) and for delaying the release of the active ingredient.

[0012] Further aspects provide onapristone ER formulations utilizing highly purified onapristone (e.g., at least about 98%). In another aspect, the ratio of onapristone to inactive excipients in the ER formulations is about 0.05 to about 5%.

[0013] In a further aspect, the AUC (area under the curve) of onapristone is at least about 1578 ng*h/ml over about an 8-12 hour period after administration of a 10 mg dose BID (i.e., twice per day) to a patient.

[0014] In another aspect, the Cmax (maximum plasma concentration) of onapristone is at least about 240 ng/ml over about an 8-12 hour period after administration of a 10 mg dose BID to a patient. In yet another aspect, a steady state plasma concentration of onapristone is achieved at about 8 days following the initial dose of the extended release onapristone pharmaceutical composition. In another aspect, the extended-release onapristone pharmaceutical composition comprises at least about 10 mg to about 50 mg of onapristone.

BRIEF DESCRIPTION OF THE DRAWINGS

[0015] Figure 1 shows the exemplary Cmax (maximum active ingredient concentration) levels per ONA dose level (10 mg, 20 mg, 30 mg, 40 mg, 50 mg extended-release BID (twice per day) and 100 mg QD (once per day));

[0016] Figure 2 shows the exemplary AUC (area under the curve) per ONA dose level (10 mg, 20 mg, 30 mg, 40 mg, 50 mg extended-release formulations BID (twice per day) and 100 mg QD (once per day));

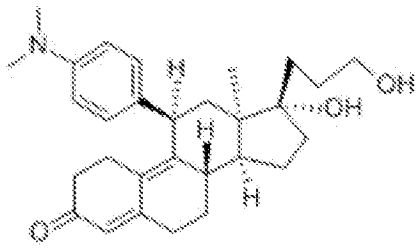
[0017] Figure 3 shows the exemplary accumulation of ONA over time per ONA dose level (10 mg, 20 mg, 30 mg, 40 mg, 50 mg extended-release formulations BID (twice per day) and 100 mg QD (once per day)); and

[0018] Figures 4A and 4B show exemplary ONA plasma levels over time per dose levels for the extended-release formulations BID (Figure 4A) and the 100 mg formulation QD.

DETAILED DESCRIPTION

[0019] Before describing several exemplary aspects described herein, it is to be understood that the invention is not limited to the details of construction or process steps set forth in the following description. The aspects described herein are capable of being practiced or being carried out in various ways.

[0020] In another aspect onapristone ER formulations comprise onapristone (ONA) ((8S,11R,13R,14S,17S)-11-[4-(dimethylamino)phenyl]-17-hydroxy-17-(3-hydroxypropyl)-13-methyl-1,2,6,7,8,11,12,14,15,16-decahydrocyclopenta[a]phenanthren-3-one), an anti-progestin drug and progesterone receptor antagonist having the following structure:

[0021] 

[0022] In one aspect, ER formulations of onapristone are provided. The term "extended release" refers to a pharmaceutical compositions or drug formulation that is administered to a patient and has a mechanism to delay the release an active ingredient (i.e., drug). For example, ER pharmaceutical compositions include the active ingredient (e.g., onapristone) and excipients that delay release of the active ingredient (e.g., hydroxypropyl methylcellulose, ethyl cellulose, Eudragit® (Evonik Industries) sustained release formulations (polymethacrylates), polyvinylpyrrolidone (PVP), carrageenan, etc.). The term "immediate release" (IR) refers to pharmaceutical compositions or drug formulations that do not have a mechanism for delaying the release of the active ingredient following administration of the formulation to a patient. Exemplary extended release formulations are provided, for example, in Table 4 herein. The terms "treat," "prevent," or similar terms, as used herein, do not necessarily mean 100% or complete treatment or prevention. Rather, these terms refer to various degrees of treatment or prevention of a particular disease (e.g., 100%, 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, 10%, 5%, or 1%) as recognized in the art as being beneficial. The terms "treatment" or "prevention" also refer to delaying onset of a disease for a period of time or delaying onset indefinitely. The term "treatment" or "treating" refers to administering a drug or treatment to a patient or prescribing a drug to a patient where the patient or a third party (e.g., caretaker, family member, or health care professional) administers the drug or treatment

[0023] One aspect provides an extended-release pharmaceutical composition comprising onapristone wherein onapristone is present in an amount from about 2 mg to about 50 mg. Onapristone can be provided, for example, in quantities of 2 mg, 2.5 mg, 5 mg, 10 mg, 20 mg, 25 mg, 37.5 mg, and 50 mg in any suitable extended release formulation (e.g., formulations of Table 4) multiple times per day (e.g., twice per day) or once per day. ER formulations can include excipients that delay the dissolution of the tablet and the subsequent release of onapristone into the gastrointestinal track which then is absorbed into the bloodstream of a patient over time

thereby reducing the C_{max} concentration compared to an IR formulation. A similar release profile can be achieved through the use of an osmotic tablet or a tablet film coated with a polymer that results in an extended release profile of the tablet.

[0024] In another aspect, onapristone ER formulations can be provided in any suitable dosage form (e.g., tablet, capsule, etc.) with a total weight of active ingredients plus excipients ranging from about 50 mg to 400 mg. In another aspect, the tablet can be a matrix tablet, film coated tablet or osmotic pump. In yet another aspect, onapristone ER formulations can be administered to a patient in need of treatment with onapristone once per day, twice per day (BID), or more to achieve the desired dose of onapristone.

[0025] Further aspects provide onapristone ER formulations wherein the purity of the onapristone is at least about 98%. Without being bound by theory, it is believed that using a highly purified form of onapristone in part decreases the liver function test abnormalities resulting in clinical benefits for cancer patients at all doses.

[0026] In another aspect, the ratio of onapristone to inactive excipients in the onapristone ER formulation is about 0.05 (e.g., Table 4) to about 5%.

[0027] Further aspects provide ER formulations wherein the AUC of onapristone following the administration of 10 mg of the onapristone ER formulation to a patient BID is at least about 1578 ng*h/ml over about 8-12 hours. In one aspect, the time period can vary by about plus or minus two hours..

[0028] Another aspect provides onapristone ER formulations where the Cmax of onapristone following the administration of 10 mg of the onapristone ER formulation to a patient BID is at least about 240 ng/ml over about 8-12 hours. In one aspect, the time period can vary by about plus or minus two hours.

[0029] Another aspect provides onapristone ER formulations where a steady state plasma concentration of onapristone is achieved at about 8 days following the administration of the onapristone ER formulations to a patient twice a day (BID).

[0030] Further aspects provide methods of administering onapristone to a patient comprising administering an onapristone ER formulation twice per day (BID) to a cancer patient, where the onapristone ER formulation comprises of at least about 10 mg to about 50 mg of onapristone. In one aspect, the ER formulation is administered once per day. In another aspect, the onapristone in the onapristone ER formulation is at least about 98% pure.

[0031] In one aspect, the onapristone administered to a patient it at least about 98% pure. In yet another aspect, onapristone in the onapristone ER formulations can be provided, for example, in quantities of 2 mg, 2.5 mg, 5 mg, 10 mg, 20 mg, 25 mg, 37.5 mg, and 50 mg.

[0032] In yet another aspect, the onapristone ER formulations can be administered twice per day (BID) to a human subject in need of treatment, where the onapristone ER formulation comprises of at least about 10 mg to about 50 mg of onapristone. In one aspect, the ER formulation is administered once per day. In another aspect, the disorder is selected from the group consisting of breast cancer, endometrial cancer, prostate cancer, ovarian, uterine endometrioid cancers, and other types of cancer which express the PR.

[0033] In another aspect, the onapristone ER formulation is administered to a human subject having a disorder capable of treatment with onapristone wherein the the AUC of onapristone following the administration of 10 mg of the onapristone ER formulation to a patient BID is at least about 1578 ng*h/ml over about 8-12 hours. In another aspect, the time period can vary by about plus or minus two hours.

[0034] In another aspect, the onapristone ER formulation is administered to a human subject having a disorder capable of treatment with onapristone by administering an onapristone ER formulation to the subject twice per day (BID) where the Cmax of onapristone in the human subject is at least about 240 ng/ml over about 8-12 hours. In another aspect, the onapristone ER formulation is administered once per day. In yet another aspect, the time period can vary by about plus or minus two hours.

[0035] In another aspect, an onapristone ER formulation is administered to a human subject having a disorder capable of treatment with onapristone twice per day (BID) where a steady state plasma concentration is achieved at about 8 days.

[0036] PK results for onapristone are available for 52 patients from the a first study (ARN-AR18-CT-101) (Table 1). Variability for onapristone PK is moderate and greater for the IR versus the ER formulation. Onapristone Cmax and AUC values for the ER form are proportional to administered dose (Figures 1 and 2). Based on observed mean AUC values, oral bioavailability for the ER versus the IR formulation is approximately 50% (Figure 24). A later Tmax value for the ER form results in somewhat lower dose-corrected Cmax values for the ER form compared to the IR form. Steady state is attained before day 8 with a mean t½ of 7.5 hrs.

[0037] Table 1 compares descriptive statistics for the primary onapristone pharmacokinetic exposure parameters following single oral doses from 10 to 50 mg of extended -release onapristone compared to that from 100 mg immediate-release onapristone (Study ARN-AR18-CT-101). Exposure following ER onapristone appears later than that for IR onapristone, consistent with extended release formulations. However, the extended-release aspects are not reflected in the overall duration of exposure. Although study size is small, onapristone exposure generally increases in proportion to ER onapristone dose. Exposure at 50 mg ER onapristone is approximately 20-50% that of 100 mg IR onapristone depending on the formulation. Variability in these parameters is similar for both formulations and across ER onapristone dose levels.

[0038] Table 1 – Summary of PK results for 52 Patients From Study ARN-AR18-CT-101

Form	**ER**	**ER**	**ER**	**ER**	**ER**	**IR**
Dose (mg)	**10**	**20**	**30**	**40**	**50**	**100**
n	**12**	**12**	**6**	**10**	**6**	**6**
AUC_{tau} (ng*h/mL)						
Mean	1578	4228	4856	6833	8966	40800
CV%	75	94	19	65	53	51
C_{max} (ng/mL)						
Mean	240	586	767	870	1459	4296
CV%	67	77	15	67	48	54
t_{max} (hrs)						
Mean	3.4	3.8	3.8	5.2	2.5	1.3
CV%	47	50	51	68	55	61
$t_{½}$ (hrs)						
Mean	8.9	7.9	3.9	23.9	11.1	23.6
CV%	120	39	31	183	140	165

[0039] PK results are available in 19 patients from a second study (ARN-AR18-CT-102) and show linear dose relationships for C_{max} and AUC (Table 2) following single oral doses from 10 to 50 mg of extended -release onapristone. Confirming the ARN-AR18-CT-101 study, the ER formulation appears to be performing according to the dose release specifications with a $t_{½}$ of approximately 8 hours and a T_{max} of approximately 3-4 hours. Steady state is also achieved within 8 days in this study. Day 29 and 57 data indicate no evidence of accumulation over time, once steady state is reached. Onapristone exposure generally increases less than proportionally with the ER onapristone dose formulation. Variability in these parameters is similar across ER onapristone dose levels.

[0040] Table 2 - Summary of PK results for 19 Patients From Study ARN-AR18-CT-102

	Onapristone ER twice-daily dose				
Parameter mean (CV%)	**10mg n=5**	**20mg n=5**	**30mg n=3**	**40mg n=3**	**50mg n=3**
T_{max}, h	4.0 (43)	3.6 (46)	4.0 (50)	3.0 (88)	3.3 (35)
C_{max}, ng/mL	260 (51)	362 (41)	325 (62)	680 (14)	538 (44)
AUC_i,ng/mL*h	7013 (53)	9745 (44)	14380 (18)	17300 (27)	23541 (39)
CL, L/h	1.85 (48)	2.04 (31)	2.13 (18)	2.18 (10)	2.4 (46)
$t_{½}$, h	5.46 (63)	5.61 (30)	9.46 (44)	5.45 (55)	15.9 (53)

[0041] Figures 1 and 2 show the results of an exemplary comparison of the relative systemic onapristone exposure following single oral doses from 10 to 50 mg of extended release onapristone compared to that from 100 mg immediate-release onapristone (Study ARN-AR18-CT-101). Onapristone exposure, assessed by Cmax (Figure 1) and AUC (Figure 2), increases linearly across the ER onapristone dose range and is lower than that for IR onapristone at all ER dose levels. Surprisingly, as disclosed herein, the ER onapristone formulations provided clinical benefit to patients despite lower onapristone exposure.

[0042] Figure 3 shows the results of an exemplary comparison of the degree of onapristone accumulation following twice-daily oral doses from 10 to 50 mg of extended -release onapristone compared to that from daily oral 100 mg immediate-release onapristone (Study ARN-AR18-CT-101). Accumulation for the ER onapristone formulation given twice daily is measurably greater than that for IR onapristone given daily.

[0043] Figures 4A and 4B show exemplary plasma onapristone concentration-time profiles for individual subjects following single oral doses of 50 mg extended -release onapristone compared to that from 100 mg immediate-release onapristone (Study ARN-AR18-CT-101). The profiles for ER onapristone generally reach maximum concentrations more slowly than those for IR onapristone, supporting the extended release of drug from the ER formulation. Concentrations

at all dose levels of ER onapristone are generally lower than those for 100 mg IR onapristone. Surprisingly, as disclosed herein, the ER onapristone formulations provided clinical benefit to patients despite lower onapristone exposure.

[0044] Table 3 – Efficacy In Study ARN-AR18-CT-101

Tumor type	**Dose**	**Response**	**% change STL**	**Duration weeks**
Serous OC	10	PR	-52	40
Serous OC	50	SD	-7	34
Granulosa OC	40	SD	-24	24
Granulosa OC	30	SD	+5	32
EC	30	SD	-13	30+
EC	20	SD	+5	32
BC	50	SD	-7	32+
BC	20	SD	NA	28
BC	40	SD	-10	24

[0045] Clinical benefit (PR (partial response or SD (stable disease) for ≥ 24 weeks) was observed in ovarian, breast and uterine endometrioid cancers using the onapristone ER formulation. One patient with serous ovarian cancer experienced a PR (32 week duration) and 8 patients had SD for at least 24 weeks (Table 3). The median progression free survival (PFS) was 57.5 days (range 21-281).

[0046] In study ARN-AR18-CT-101, in 52 female patients with PR-positive solid tumors, 9/46 patients (20%) receiving the onapristone ER formulation at doses from 10-50 mg BID demonstrated clinical benefit, vs. 0/6 (0%) patients receiving the 100mg once-daily onapristone IR formulation. Clinical benefit responses, defined as RECIST 1.1 partial response or stable disease for at least 24 weeks, were seen only in patients receiving ER. Of interest, 7/9 of the

patients with clinical benefit (78%) received doses below the established 100mg IR dose and the patient with a partial response was treated at the lowest ER dose level, 10mg BID.

[0047] With respect to ARN-AR18-CT-102, 2 of 21 patients with prostate cancer had SD after week 12. Median duration of treatment was 8 weeks.

EXAMPLES

[0048] The following non-limiting examples illustrate aspects described herein. Not every element described herein is required. Indeed, a person of skill in the art will find numerous additional uses of and variations to the methods described herein, which the inventors intend to be limited only by the claims. All references cited herein are incorporated by reference in their entirety.

[0049] Example 1

[0050] ER Formulations

[0051] **Table 4 – Onapristone Extended-Release Formulations**

Component	**Amount per tablet (mg)**				**Function**
	2.5 mg	**5 mg**	**10 mg**	**20 mg**	
Onapristone	2.50	5.00	10.00	20.00	Active
Lactose monohydrate	10.25	20.50	41.00	82.00	Filler
Microcrystalline cellulose	10.25	20.50	41.00	82.00	Filler
Pregelatinized starch	10.00	20.00	40.00	80.00	Disintegrant
Hydroxypropyl methylcellulose	16.50	33.00	66.00	132.00	Binder / modified release agent
Colloidal silicon dioxide	0.25	0.50	1.00	2.00	Glidant
Magnesium stearate	0.25	0.50	1.00	2.00	Lubricant
Tablet weight (mg)	50.00	100.00	200.00	400.00	

[0052] Table 4 provide exemplary onapristone extended release formulations. In one aspect, the tablets can be provided to a patient alone or in any desired combination to achieve the desired dose.

[0053] Example 2 – Preparing Exemplary Onapristone ER Formulations

[0054] Onapristone extended-release formulations can be prepared by the following exemplary method:

[0055] Step 1: De-lump onapristone drug substance by milling or by passing through a wire screen followed by further passing the resulting de-lumped onapristone through a wire screen of appropriate mesh size (e.g., 425 or 710 microns).

[0056] Step 2: Screen the colloidal silicon dioxide and approximately half of the pregelatinized starch separately through a screen of appropriate mesh size (e.g., 425 or 710 microns) into a stainless steel blending container. The previously-screened onapristone drug substance from Step 1 is added to this blend.

[0057] Step 3: The mixture is blended and screened through a screen of appropriate mesh size (e.g., 425 or 710 microns).

[0058] Step 4: The remaining pregelatinized starch is screened through a screen of appropriate mesh size (e.g., 425 or 710 microns) into the stainless steel blending container (from Step 2). The previously screened mixture from Step 3 is added to the container.

[0059] Step 5: The mixture is blended to achieve a homogenous mix.

[0060] Step 6: Approximately half of the microcrystalline cellulose, half of the lactose monohydrate and half of the hydroxypropyl methylcellulose are separately screened into a larger stainless steel blending container through a screen of appropriate mesh size (e.g., 425 or 710 microns). The blend from Step 5 is added to this container, and the remaining microcrystalline cellulose, lactose monohydrate and hydroxypropyl methylcellulose are screened into the container through a screen of appropriate mesh size (e.g., 425 or 710 microns).

[0061] Step 7: The mixture is blended further to achieve a homogeneous mix.

[0062] Step 8: The mixture from Step 7 is co-screened with magnesium stearate through a screen of appropriate mesh size (e.g., 425 or 710 microns) into the container from Step 4.

[0063] Example 3

[0064] Patients and Methods

[0065] *Eligibility*

[0066] Inclusion criteria included:

[0067] (1) post-menopausal female patients ≥ 18 years of age that have been previously treated recurrent or metastatic progesterone receptor-expressing cancer (e.g., endometrial, ovarian, breast cancer or uterine sarcoma) with evaluable disease per Response Evaluation Criteria In Solid Tumors, version 1.1 (RECIST 1.1);

[0068] (2) patients having available tissue blocks or biopsy specimens to determine progesterone receptor (PR) and activated progesterone receptor (APR) status; and

[0069] (3) patients having Eastern Cooperative Oncology Group (ECOG) performance status 0-1, and signed informed consent.

[0070] The PR determination for inclusion purposes was performed on archived tissue blocks in the pathology department of each participating center. Central PR/APR evaluation was planned, but retrospective relative to inclusion and treatment.

[0071] Key exclusion criteria included significantly impaired liver or kidney function, creatinine clearance lower than 60 mL/min, total bilirubin > upper limit of normal (ULN), alkaline phosphatase > ULN (or > 2.5 x ULN with liver or > 5 x ULN with bone metastases), ALT/AST > ULN (or > 2.5 x ULN with liver metastases), QTcF > 480 msec, chronic inflammatory liver condition, severe concomitant disease, uncontrolled brain metastases, inadequate washout from previous therapy, inability to swallow or absorb tablets, use of inhibitors, inducers or substrates of CYP3A4, or use of progestin-based hormone replacement therapy.

[0072] Example 4

[0073] Study Design and Treatment

[0074] The study was an open-label, multicenter, randomized, parallel-group, two part phase 1-2 study with phase I part of the trial discussed herein. To determine the recommended phase 2 dose (RP2D), patients enrolled in this phase 1 study were randomized in parallel fashion to six (6) cohorts: five (5) cohorts of ER ONA tablets (10 mg BID, 20 mg BID, 30 mg BID, 40 mg BID, 50 mg BID) and one (1) cohort using the IR tablet formulation (100 mg QD). The trial was conducted in five (5) centers in France (registered on ClinicalTrials.gov as NCT02052128).

[0075] The study was approved by the Ile de France III Comité pour la Protection des Personnes (a French national ethics committee), the ANSM (French regulatory authority) and individual site scientific review boards, and written informed consent was obtained from each study patient.

[0076] Highly purified ONA tablets can be by standard pharmaceutical chemistry purification methods by those skilled in the art. ER formulation with release kinetics from 10-12 hours depending on tablet dose. The original study design included a 20-patient expansion component. An 8-week dose-limiting toxicity (DLT) observation period was utilized to characterize thoroughly the safety profile, as previous ONA studies demonstrated a spike in the LFTs at approximately 6 weeks of treatment.

[0077] Patients were treated until documented progressive disease (PD) or intolerance to medication. We consider the design of this study to be in agreement with the recently-proposed guidance for phase 1 protocols for dose escalation [Iasonos 2015].

[0078] Example 5

[0079] Pharmacokinetics Methods

[0080] Blood samples were collected at 0, 1, 2, 3, 4, 6, 8, 12 (before next BID dose), and 24 (before next dose- for 100 mg IR only) hours post- ONA, as well as hour 0 on days 8, 29 and 57 (just before drug intake). Plasma concentrations of ONA, mono-demethylated onapristone (M1) and other metabolites in plasma and urine were analyzed with a validated ultra-performance liquid chromatography with tandem mass spectrometry detection (UPLC-MS/MS) assay.

Pharmacokinetic modeling was performed using Monolix software in order to estimate PK parameters Cmax, Tmax, AUC0-last, AUC0-8, t1/2, Vd, CL, and Vc.

[0081] Although the above description refers to particular aspects, it is to be understood that these aspects are merely illustrative. It will be apparent to those skilled in the art that various modifications and variations can be made to the polymorphic forms and methods described herein. Thus, it is intended that the present description include modifications and variations that are within the scope of the appended claims and their equivalents.

REFERENCES

1. Afhüppe W, Sommer A, Muller J et al. Global gene expression profiling of progesterone receptor modulators in T47D cells provides a new classification system. J Steroid Biochem Mol Biol 2009;113:101-115.

2. Arnett-Mansfield RL, DeFazio A, Mote PA et al. Sub-nuclear Distribution of Progesterone Receptors A and B in Normal and Malignant Endometrium. The Journal of Clinical Endocrinology & Metabolism 2004; 89: 1429-1442.

3. Beck CA, Zhang Y, Weigel N et al. Two Types of Anti-progestins Have Distinct Effects on Site-specific Phosphorylation of Human Progesterone Receptor. The Journal of Biological Chemistry 1996;271:1209-1217.

4. Benagiano G, Bastianelli C, Farris M. Selective progesterone receptor modulators 3: use in oncology, endocrinology and psychiatry. Expert Opin. Pharmacother 2008; 9:2487-2496.

5. Blankenstein MA, Verheijen FM, Jacobs JM et al. Occurrence, regulation, and significance of progesterone receptors in human meningioma. Steroids 2000; 65: 795–800

6. Bonkhoff H, Fixemer T, Hunsicker I, and Remberger K. Progesterone Receptor Expression in Human Prostate Cancer: Correlation With Tumor Progression. Prostate 2001; 48:285-291.

7. Bonneterre J, Hutt E, Bosq J et al. Development of a technique to detect the activated form of the progesterone receptor and correlation with clinical and histopathological characteristics of endometrioid adenocarcinoma of the uterine corpus. Gynecologic Oncology 2015; doi:10.1016/j.ygyno.2015.06.037

8. Cameron S, Critchley HOD, Buckley CH et al. The effects of post-ovulatory administration of onapristone on the development of a secretory endometrium. Human Reproduction 1996; 11 (1):40-49.

9. Cameron ST, Glasier AF, Narvekar N et al. Effects of onapristone on postmenopausal endometrium. Steroids 2003;68:1053–1059.

10. Cottu P, A Italiano, A Varga et al. Onapristone (ONA) in progesterone receptor (PR)-expressing tumors: Efficacy and biomarker results of a dose-escalation phase 1 study. J Clin Oncol 2015;33 (suppl; abstr 5593).

11. Croxatto H, Salvatierra AA, Fuentealba B et al. Effect of the antiprogestin onapristone on follicular growth in women. Human Reproduction 1994; 9: 1442-1447.

12. Goyeneche AA and Telleria CM. Antiprogestins in gynecological diseases. Reproduction 2015 149 : R15–R33.

13. Graham D, Bosq J, Caillaud JM et al. Determination of the activated form of the progesterone receptor (PR) in endometrial cancer (EC). J Clin Oncol 2013; 31(suppl; abstr 5602).

14. Hopp TA, Weiss HL, Hilsenbeck SG, et al. Breast Cancer Patients with Progesterone Receptor PR-A-Rich Tumors Have Poorer Disease-Free Survival Rates. Clin Cancer Res 2004 10; 2751

15. Hutt E, Bosq J, Powell MA, Leblanc E, Fujiwara K, Herzog TJ, Coleman RL, Graham D, Clarke C, Gilles EM, Zukiwski AA, Monk BJ. Clinical and pathological correlation of the activated form of the progesterone receptor (APR) in Endometrial Cancer (EC). ECC 2013, #1.002

16. Iasonos A, Gönen M, Bosl GJ. Scientific Review of Phase I Protocols With Novel Dose-Escalation Designs: How Much Information Is Needed? Journal of Clinical Oncology 2015:JCO. 2014.59. 8466.

17. Ishibashi H, Suzuki T, Suzuki S, et al. Progesterone receptor in non-small cell lung cancer--a potent prognostic factor and possible target for endocrine therapy. Cancer Res 2005;65(14):6450-8.

18. Jonat W, Giurescu M, Robertson JFR. The clinical efficacy of progesterone antagonists in breast cancer. Endocrine Ther Breast Cancer 2002 (8):117-124.

19. Jonat W, Bachelot T, Ruhstaller P et al. Randomized phase 2 study of lonaprisan as second line therapy for progesterone receptor positive breast cancer. Ann Oncol 2013; 24: 2543–2548.

20. Kim JJ, Kurita T, and Bulun SE. Progesterone Action in Endometrial Cancer, Endometriosis, Uterine Fibroids, and Breast Cancer. Endocrine Rev 2013; 34: 130–162.

21. Klijn JGM, Setyono-Han B, Foekens JA. Progesterone antagonists and progesterone receptor modulators in the treatment of breast cancer. Steroids 2000; 65: 825-830.

22. Koivisto-Korander R, Leminen A and Heikinheimo O. Mifepristone as treatment of recurrent progesterone receptor-positive uterine leiomyosarcoma. Obstetrics and Gynecology 2007; 109: 512–514.

23. Lanari C, Wargon V, Rojas P and Molinolo AA. Antiprogestins in breast cancer treatment: are we ready? Endocrine-Related Cancer 2012; 19: R35–R50.

24. Lange CA, Gioeli D, Hammes SR, and PC Marker. Integration of Rapid Signaling Events with Steroid Hormone Receptor Action in Breast and Prostate Cancer. Annu Rev Physiol 2007; 69:171–99.

25. Lange CA, Sartorius CA, Abdel-Hafiz H, et al. Progesterone Receptor Action: Translating Studies in Breast Cancer Models to Clinical Insights. Innov Endocrinol Cancer 2008; 7: 94-110.

26. Mortel R, Zaino R, and Satyaswaroop PG. Heterogeneity and Progesterone- Receptor Distribution in Endometrial Adenocarcinoma. Cancer 1984; 53:113-116.

27. Mote P and Clarke C. Relative expression of progesterone receptors A and B in premalignant and invasive breast lesions. Breast Cancer Research 2000; 2 (Suppl 1): P2.01 doi:10.1186/bcr103.

28. Mote PA, Bartow S, Tran N, Clarke CL. Loss of co-ordinate expression of progesterone receptors A and B is an early event in breast carcinogenesis. Breast Cancer Res Treat 2002;72(2):163-72.

29. Mote PA, Graham JD, Clarke CL. Progesterone receptor isoforms in normal and malignant breast. Ernst Schering Found Symp Proc. 2007;(1):77-107.

30. Mueller MD, Vigne JL, Pritts EA et al. Progestins activate vascular endothelial growth factor gene transcription in endometrial adenocarcinoma cells. Fertil Steril 2003;79: 386- 392.

31. Rezai K, Cottu PH, Huguet S et al. Population pharmacokinetic (PPK) modeling of onapristone in patients (pts) with progesterone receptor (PR)-expressing cancers. AACR Annual Meeting 2015. Abstract 4523.

32. Robertson JFR, Willsher PC, Winterbottom L et al. Onapristone, a Progesterone Receptor Antagonist, as First-line Therapy in Primary Breast Cancer. Eur J Cancer 1999; 35: 214-218.

33. Sieh W, Köbel M, Longacre TA, et al. Hormone-receptor expression and ovarian cancer survival: an Ovarian Tumor Tissue Analysis consortium study. Lancet Oncol 2013; http://dx.doi.org/10.1016/S1470-2045(13)70253-5.

34. Taplin ME, Manola J, Oh W et al. A phase II study of mifepristone (RU-486) in castration-resistant prostate cancer, with a correlative assessment of androgen-related hormones. J Compil BJU Int 2008; 101: 1084-1089.

35. Thigpen JT, Brady M, Alvarez R et al. Oral Medroxyprogesterone Acetate in the Treatment of Advanced or Recurrent Endometrial Carcinoma: A Dose-Response Study by the Gynecologic Oncology Group. J Clin Oncol 1999; 17: 1736-1744.

36. Yin P, Lin Z, Reierstad S, et al. Transcription Factor KLF11 Integrates Progesterone Receptor Signaling and Proliferation in Uterine Leiomyoma Cells. Cancer Res 2010; 70(4); 1722–30.

CLAIMS

What is claimed is:

1. An extended release pharmaceutical composition comprising onapristone wherein onapristone is present in an amount from about 2 mg to about 50 mg.

2. The extended release pharmaceutical composition of claim 1, wherein the dosage form of the pharmaceutical composition is selected from the group consisting of tablets and capsules.

3. The extended release pharmaceutical composition of claim 1, wherein the purity of the onapristone is at least about 98%.

4. The extended-release pharmaceutical composition of claim 1, wherein the ratio of onapristone to inactive excipients is about 0.05 to about 5%.

5. The extended release pharmaceutical composition of claim 1, wherein the onapristone is present in an amount selected from the group consisting of about 2 mg, 2.5 mg, 5 mg, 10 mg, 20 mg, 25 mg, 37.5 mg, and 50 mg.

6. The extended release pharmaceutical composition of claim 1, wherein the AUC of onapristone following the administration of 10 mg of the extended release formulation to a patient twice per day is at least about 1578 ng*h/ml over about 8-12 hours.

7. The extended release pharmaceutical composition of claim 1, wherein the Cmax of onapristone following the administration of 10 mg of the extended release formulation to a patient twice per day is at least about 240 ng/ml over about 8-12 hours.

8. The extended release pharmaceutical composition of claim 1, wherein a steady state plasma concentration is achieved at about 8 days following the administration of the extended release pharmaceutical composition to a patient twice per day.

9. A method of administering onapristone to a patient having cancer comprising administering an extended release onapristone pharmaceutical composition twice per day to the patient, wherein the extended release onapristone pharmaceutical composition comprises of at least about 2 mg to about 50 mg of onapristone.

10. The method of claim 9, wherein the extended release onapristone pharmaceutical composition is administered once per day.

11. The method of claim 9, wherein the onapristone it at least about 98% pure.

12. The method of claim 9, wherein the amount of onapristone in the extended release onapristone pharmaceutical composition is selected from the group consisting of about 2 mg, 2.5 mg, 5 mg, 10 mg, 20 mg, 25 mg, 37.5 mg and 50 mg.

13. The method of claim 9, wherein the cancer expresses the progesterone receptor.

14. The method of claim 13, wherein the cancer is selected from the group consisting of breast, prostate, ovarian, and uterine endometrioid cancers.

15. A method of treating a human subject having a disorder capable of treatment with onapristone comprising administering the extended release onapristone pharmaceutical composition of claim 1 to the human subject twice per day, wherein the AUC of onapristone following the administration of 10 mg of the extended release formulation to a patient twice per day is at least about 1578 ng*h/ml over about 8-12 hours.

16. The method of claim 15, wherein the extended release onapristone pharmaceutical composition is administered to the human subject once per day.

17. A method of treating a human subject having a disorder capable of treatment with onapristone comprising administering to said subject 10 mg of the extended release onapristone pharmaceutical composition of claim 1 twice per day, wherein the Cmax of onapristone in the human subject is at least about 240 ng/ml over about 8-12 hours.

18. The method of claim 17, wherein the extended release onapristone pharmaceutical formulation is administered to the human subject once per day.

19. A method of treating a human subject having a disorder capable of treatment with onapristone comprising administering to said subject the extended release pharmaceutical composition of claim 1 twice per day, wherein a steady state plasma concentration is achieved at about 8 days.

20. The method of claim 19, wherein the extended release onapristone pharmaceutical formulation is administered to the human subject once per day.

Figure 1

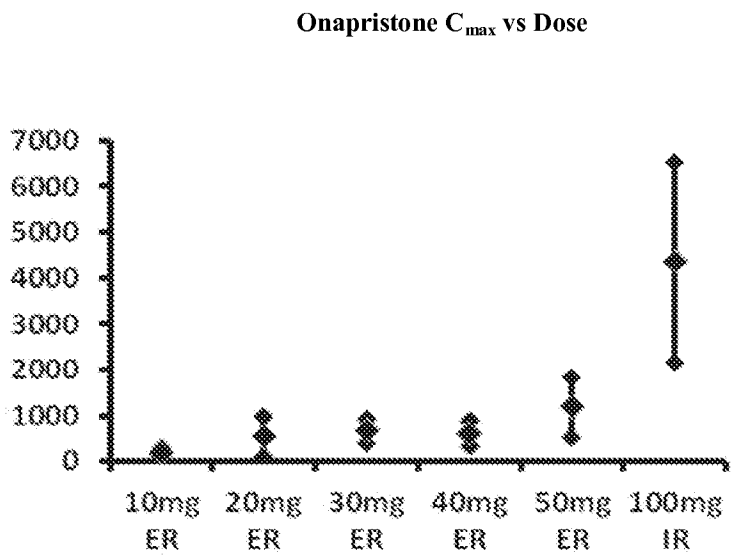

Onapristone C_{max} vs Dose
7000
6000
5000
4000
3000
2000
1000
0
10mg ER
20mg ER
30mg ER
40mg ER
50mg ER
100mg IR

Figure 2

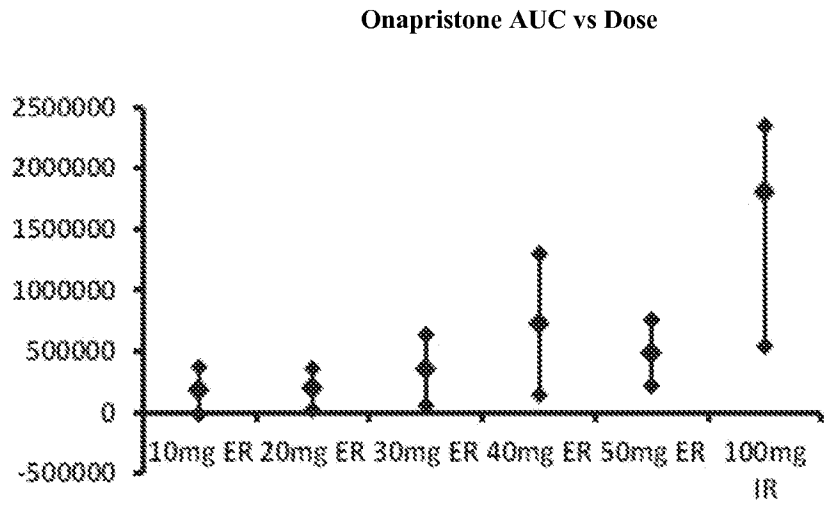

Onapristone AUC vs Dose
2500000
2000000
1500000
1000000
500000
0
-500000
10mg ER
20mg ER
30mg ER
40mg ER
50mg ER
100mg IR

Figure 3

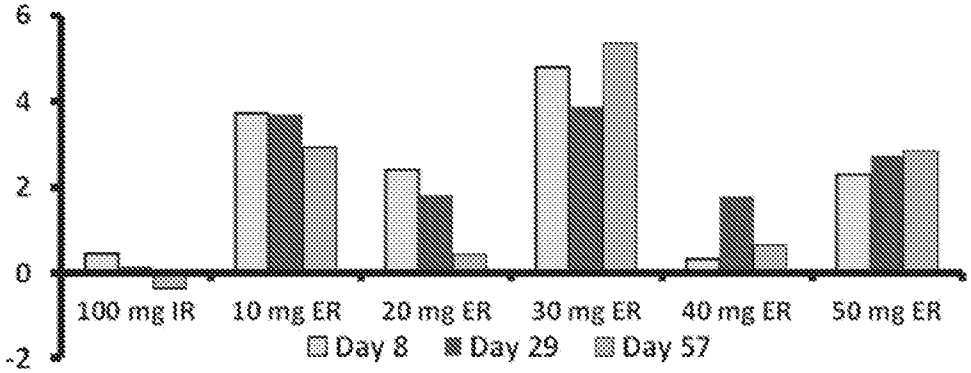

6
4
2
0
-2
100 mg IR
10 mg ER
20 mg ER
30 mg ER
40 mg ER
50 mg ER
Day 8
Day 29
Day 57

Figure 4A

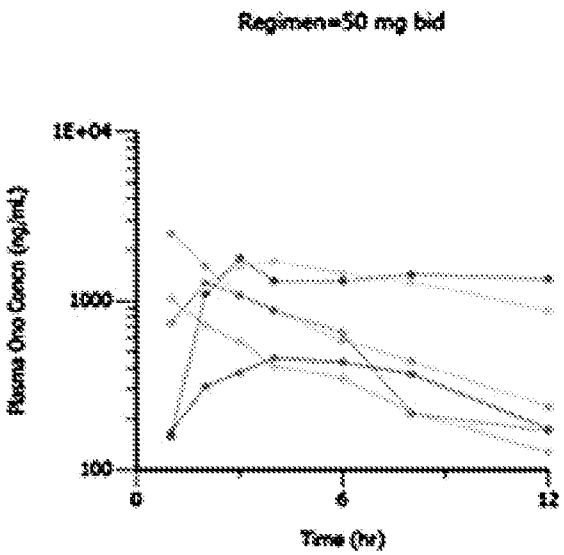
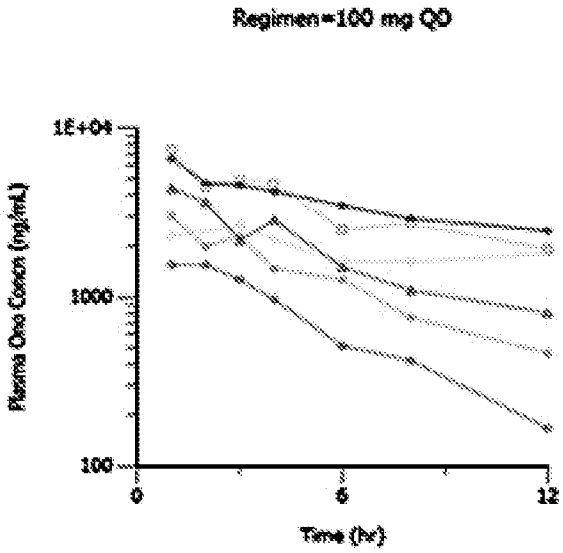


Figure 4B



INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2015/060940

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/56 (2016.01)
CPC - A61K 31/56 (2015.12)
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)
IPC(8) - A61K 31/56, 31/575, 45/06; C07J 41/00 (2016.01)
CPC - A61K 31/56, 31/575, 45/06; C07J 41/00 (2015.12)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 424/450; 514/110, 170, 179; IPC(8) - A61K 31/56, 31/575, 45/06; C07J 41/00; CPC - A61K 31/56, 31/575, 45/06; C07J 41/00 (keyword delimited)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Orbit, Google Patents, Google Scholar.
Search terms used: onapristone, cancer.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2014/0271819 A1 (PRONIUK) 18 September 2014 (18.09.2014) entire document	1, 2, 4, 5, 9, 10, 12-14
---		---
Y		3, 6-8, 11, 15-20
Y	US 2013/0029953 A1 (NICKISCH et al) 31 January 2013 (31.01.2013) entire document	3, 11
Y	US 2011/0293511 A1 (JOHNS et al) 01 December 2011 (01.12.2011) entire document	6, 7, 15-18
Y	US 2012/0230983 A1 (MULLER et al) 13 September 2012 (13.09.2012) entire document	8, 19, 20

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" 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
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
07 January 2016	28 JAN 2016
Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, VA 22313-1450 Facsimile No. 571-273-8300	Authorized officer Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774