FULL PRESCRIBING INFORMATION

RUBRACA 200 MG
Each film coated tablet contains rucaparib camsylate corresponding to 200 mg rucaparib

RUBRACA 250 MG
Each film coated tablet contains rucaparib camsylate corresponding to 250 mg rucaparib

RUBRACA 300 MG
Each film coated tablet contains rucaparib camsylate corresponding to 300 mg rucaparib

1 INDICATIONS AND USAGE

1.1 Maintenance Treatment of Recurrent Ovarian Cancer

Rubraca is indicated for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy

1.2 Treatment of BRCA-mutated Ovarian Cancer After 2 or More Chemotherapies

Rubraca is indicated for the treatment of adult patients with a deleterious *BRCA* mutation (germline and/or somatic)-associated epithelial ovarian, fallopian tube, or primary peritoneal cancer who have been treated with two or more chemotherapies.

2 DOSAGE AND ADMINISTRATION

2.1Patient Selection for Treatment of BRCA-mutated Ovarian Cancer

Select patients for the treatment of epithelial ovarian, fallopian tube, or primary peritoneal cancer with Rubraca based on the presence of a deleterious *BRCA* mutation (germline and/or somatic*) [see Indications and Usage (1.2) and Clinical Studies (14.2)]*.

2.2 Recommended Dose

The recommended dose of Rubraca is 600 mg (two 300 mg tablets) taken orally twice daily with or without food, for a total daily dose of 1,200 mg.

Continue treatment until disease progression or unacceptable toxicity.

If a patient misses a dose of Rubraca, instruct the patient to take the next dose at its scheduled time. Vomited doses should not be replaced.

2.3 Dose Modifications for Adverse Reactions

To manage adverse reactions, consider interruption of treatment or dose reduction. Recommended Rubraca dose modifiactions for adverse reactions are indicated in Table 1.

Table 1. Recommended Dose Modifications for Adverse Reactions

Dose Reduction	Dose
Starting Dose	600 mg twice daily (two 300 mg tablets)
First Dose Reduction	500 mg twice daily (two 250 mg tablets)
Second Dose Reduction	400 mg twice daily (two 200 mg tablets)
Third Dose Reduction	300 mg twice daily (one 300 mg tablet)

3 DOSAGE FORMS AND STRENGTHS

- Tablets (200 mg): blue, round, immediate-release, film-coated, debossed with “C2”.
- Tablets (250 mg): white, diamond, immediate-release, film-coated, debossed with “C25”.
- Tablets (300 mg): yellow, oval, immediate-release, film-coated, debossed with “C3”.

4 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients listed in section 11.

5 WARNINGS AND PRECAUTIONS

5.1 Myelodysplastic Syndrome/Acute Myeloid Leukemia

Myelodysplastic Syndrome (MDS)/Acute Myeloid Leukemia (AML) occur in patients treated with Rubraca, and are potentially fatal adverse reactions. In 1146 treated patients, *[see Adverse Reactions (6.1)]*, MDS/AML occurred in 20 patients (1.7%), including those in long term follow-up. Of these, 8 occurred during treatment or during the 28 day safety follow-up (0.7%). The duration of Rubraca treatment prior to the diagnosis of MDS/AML ranged from 1 month to approximately 53 months. The cases were typical of secondary MDS/cancer therapy-related AML; in all cases, patients had received previous platinum-containing chemotherapy regimens and/or other DNA damaging agents.

In TRITON2, MDS/AML was not observed in patients with mCRPC (n=209) regardless of homologous recombination deficiency (HRD) mutation *[see Adverse Reactions (6.1)]*.

Do not start Rubraca until patients have recovered from hematological toxicity caused by previous chemotherapy (≤ Grade 1). Monitor complete blood counts for cytopenia at baseline and monthly thereafter for clinically significant changes during treatment. For prolonged hematological toxicities (> 4 weeks), interrupt Rubraca or reduce dose according to Table 1 *[see Dosage and Administration (2.3)]* and monitor blood counts weekly until recovery. If the levels have not recovered to Grade 1 or less after 4 weeks or if MDS/AML is suspected, refer the patient to a hematologist for further investigations, including bone marrow analysis and blood sample for cytogenetics. If MDS/AML is confirmed, discontinue Rubraca.

5.2 Embryo-Fetal Toxicity

Rubraca can cause fetal harm when administered to a pregnant woman based on its mechanism of action and findings from animal studies. In an animal reproduction study, administration of rucaparib to pregnant rats during the period of organogenesis resulted in embryo-fetal death at exposures that were 0.04 times the $AUC_{0\text{-}24h}$ in patients receiving the recommended human dose of 600 mg twice daily. Apprise pregnant women of the potential risk to a fetus. Advise females

of reproductive potential to use effective contraception during treatment and for 6 months following the last dose of Rubraca *[see Use in Specific Populations (8.1, 8.3) and Clinical Pharmacology (12.1)]*.

Based on findings from genetic toxicity and animal reproduction studies, advise male patients with female partners of reproductive potential or who are pregnant to use effective contraception during treatment and for 3 months following the last dose of Rubraca *[see Use in Specific Populations (8.1, 8.3)]*.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:

- Myelodysplastic Syndrome/Acute Myeloid Leukemia *[see Warnings and Precautions (5.1)]*.

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form:

https://sideeffects.health.gov.il/

and emailed to the Registration Holder's Patient Safety Unit at: drugsafety@neopharmgroup.com

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.The pooled safety population in the WARNINGS AND PRECAUTIONS section reflect exposure to Rubraca at 600 mg BID in 1146 patients in Study10 (CO-338-010), ARIEL2, ARIEL3, and TRITON2.

Maintenance Treatment of Recurrent Ovarian Cancer

The safety of Rubraca for the maintenance treatment of patients with epithelial ovarian, fallopian tube, or primary peritoneal cancer was investigated in ARIEL3, a randomized (2:1), double-blind, placebo-controlled study in which 561 patients received either Rubraca 600 mg BID (n=372) or placebo (n=189) until disease progression or unacceptable toxicity. The median duration of study treatment was 8.3 months (range: < 1 month to 35 months) for patients who received Rubraca and 5.5 months for patients who received placebo.

Dose interruptions due to an adverse reaction of any grade occurred in 65% of patients receiving Rubraca and 10% of those receiving placebo; dose reductions due to an adverse reaction occurred in 55% of Rubraca patients and 4% of placebo patients. The most frequent adverse reactions leading to dose interruption or dose reduction of Rubraca were thrombocytopenia (18%), anemia (17%), nausea (15%), and fatigue/asthenia (13%). Discontinuation due to adverse reactions occurred in 15% of Rubraca patients and 2% of placebo patients. Specific adverse reactions that most frequently led to discontinuation in patients treated with Rubraca were anemia (3%), thrombocytopenia (3%) and nausea (3%). Table 2 describes the adverse reactions occurring in ≥20% of patients; while Table 3 describes the laboratory abnormalities occurring in ≥25% of patients occurring in ARIEL3.

Table 2. Adverse Reactions in ARIEL3 Occurring in ≥ 20% of Patients

Adverse reactions	Rubraca N=372		Placebo N=189	
	Grades[a] 1-4 %	Grades 3-4 %	Grades[a] 1-4 %	Grades 3-4 %
Gastrointestinal Disorders				
Nausea	76	4	36	0.5
Abdominal pain/distention[b]	46	3	39	0.5
Constipation	37	2	24	1
Vomiting	37	4	15	1
Diarrhea	32	0.5	22	1
Stomatitis[b]	28	1	14	0.5
General Disorders and Administration Site Conditions				
Fatigue/asthenia	73	7	46	3
Skin and Subcutaneous Tissue Disorders				
Rash[b]	43	1	23	0
Nervous System Disorders				
Dysgeusia	40	0	7	0
Investigations				
AST/ALT elevation	38	11	4	0
Blood and Lymphatic System Disorders				
Anemia	39	21	5	0.5
Thrombocytopenia	29	5	3	0
Neutropenia	20	8	5	1
Respiratory, Thoracic, and Mediastinal Disorders				
Nasopharyngitis/Upper respiratory tract infection[b]	29	0.3	18	1
Metabolism and Nutrition Disorders				
Decreased appetite	23	1	14	0

[a] National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE version 4.03)
[b] Consists of grouped related terms that reflect the medical concept of the adverse reaction

Adverse reactions occurring < 20% of patients treated with Rubraca include headache (18%), dizziness (19%), dyspepsia (19%), insomnia (15%), dyspnea (17%), pyrexia (13%), peripheral edema (11%), and depression (11%).

Table 3. Laboratory Abnormalities in ARIEL3 Occurring in ≥ 25% of Patients

Laboratory Parameter[a]	Rubraca N=372		Placebo N=189	
	Grade 1-4 %	Grade 3-4 %	Grade 1-4 %	Grade 3-4 %
Chemistry				
Increase in creatinine	98	0.3	90	0
Increase in cholesterol	84	4	78	0
Increase in ALT	73	7	4	0
Increase in AST	61	1	4	0
Increase in Alkaline Phosphatase	37	0.3	10	0
Hematology				
Decrease in hemoglobin	88	13	56	1
Decrease in platelets	44	2	9	0
Decrease in leukocytes	44	3	29	0
Decrease in neutrophils	38	6	22	3
Decrease in lymphocytes	29	5	20	3

[a] Patients were allowed to enter clinical studies with laboratory values of CTCAE Grade 1.

Treatment of BRCA-mutated Recurrent Ovarian Cancer After 2 or More Chemotherapies

Rubraca 600 mg twice daily as monotherapy has also been studied in 377 patients with epithelial ovarian, fallopian tube or primary peritoneal cancer who have progressed after 2 or more prior chemotherapies in two open-label, single arm trials, study 10 and ARIEL2. In these patients, the median age was 62 years (range: 31 to 86), 100% had an ECOG performance status of 0 or 1, 38% had *BRCA*-mutated ovarian cancer, 45% had received 3 or more prior lines of chemotherapy, and the median time since ovarian cancer diagnosis was 43 months (range: 6 to 197). Table 4 describes the adverse reactions occurring in ≥20% of patients; while Table 5 describes the laboratory abnormalities occurring in ≥35% of patients occurring in ARIEL2.

Table 4. Adverse Reactions Reported in ≥ 20% of Patients with Ovarian Cancer After ≥ 2 Chemotherapies Treated with Rubraca in Study 10 and ARIEL 2

Adverse Reaction	All Ovarian Cancer Patients (N = 377)	
	Grades[a] 1-4 (%)	Grades 3-4 (%)
Gastrointestinal Disorders		
Nausea	77	5
Vomiting	46	4
Constipation	40	2
Diarrhea	34	2
Abdominal Pain	32	3
General Disorders		
Asthenia/Fatigue	77	11
Blood and Lymphatic System Disorders		
Anemia	44	25
Thrombocytopenia	21	5
Nervous System Disorders		
Dysgeusia	39	0.3
Metabolism and Nutrition Disorders		
Decreased appetite	39	3
Respiratory, Thoracic, and Mediastinal Disorders		
Dyspnea	21	0.5

[a] National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE version 4.03)

The following adverse reactions have been identified in < 20% of the 377 patients treated with Rubraca 600 mg twice daily: dizziness (17%), neutropenia (15%), rash (includes rash, rash erythematous, rash maculopapular and dermatitis) (13%), pyrexia (11%), photosensitivity reaction (10%), pruritus (includes pruritus and pruritus generalized) (9%), hypersensitivity (includes flushing, wheezing, eyelid edema, drug hypersensitivity, face edema, swelling face) (4%), palmar-plantar erythrodysaesthesia syndrome (2%), and febrile neutropenia (1%).

Table 5. Laboratory Abnormalities Reported in ≥ 35% of Patients with Ovarian Cancer After ≥ 2 Chemotherapies Treated with Rubraca in Study 10 and ARIEL 2

	All Patients with Ovarian Cancer (N = 377) %	
Laboratory Parameter	**Grade 1-4 [a]**	**Grade 3-4**
Clinical Chemistry		
Increase in creatinine	92	1
Increase in ALT[b]	74	13
Increase in AST[b]	73	5
Increase in cholesterol	40	2
Hematologic		
Decrease in hemoglobin	67	23
Decrease in lymphocytes	45	7
Decrease in platelets	39	6
Decrease in absolute neutrophil count	35	10

[a] At least one worsening shift in CTCAE grade and by maximum shift from baseline.
[b] Increase in ALT/AST led to treatment discontinuation in 0.3% of patients (1/377).

7 DRUG INTERACTIONS

7.1 Effect of Rubraca on Other Drugs

Certain CYP1A2, CYP3A, CYP2C9, or CYP2C19 Substrates

Concomitant administration of Rubraca with CYP1A2, CYP3A, CYP2C9, or CYP2C19 substrates can increase the systemic exposure of these substrates *[see Clinical Pharmacology (12.3)]*, which may increase the frequency or severity of adverse reactions of these substrates.

If concomitant administration is unavoidable between Rubraca and substrates of these enzymes where minimal concentration changes may lead to serious adverse reactions, decrease the substrate dosage in accordance with the approved prescribing information.

If concomitant administration with warfarin (a CYP2C9 substrate) cannot be avoided, consider increasing the frequency of international normalized ratio (INR) monitoring.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from animal studies and its mechanism of action, Rubraca can cause fetal harm when administered to pregnant women. There are no available data in pregnant women to inform the drug-associated risk. In an animal reproduction study, administration of rucaparib to pregnant rats during organogenesis resulted in embryo-fetal death at maternal exposures that were 0.04 times the $AUC_{0\text{-}24h}$ in patients receiving the recommended dose of 600 mg twice daily *[see Data]*. Apprise pregnant women of the potential risk to a fetus.

Data

Animal Data

In a dose range-finding embryo-fetal development study, pregnant rats received oral doses of 50, 150, 500, or 1000 mg/kg/day of rucaparib during the period of organogenesis. Post-implantation loss (100% early resorptions) was observed in all animals at doses greater than or equal to 50 mg/kg/day (with maternal systemic exposures approximately 0.04 times the human exposure at the recommended dose based on $AUC_{0\text{-}24h}$).

8.2 Lactation

Risk Summary

There is no information regarding the presence of rucaparib in human milk, or on its effects on milk production or the breast-fed child. Because of the potential for serious adverse reactions in breast-fed children from Rubraca, advise lactating women not to breastfeed during treatment with Rubraca and for 2 weeks following the last dose.

8.3 Females and Males of Reproductive Potential

Rubraca can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*.

Pregnancy Testing

Pregnancy testing is recommended for females of reproductive potential prior to initiating Rubraca.

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment and for 6 months following the last dose of Rubraca *[see Use in Specific Populations (8.1)]*.
Males

Based on findings in genetic toxicity and animal reproduction studies, advise male patients with female partners of reproductive potential or who are pregnant to use effective methods of contraception during treatment and for 3 months following last dose of Rubraca. Advise male patients not to donate sperm during therapy and for 3 months following the last dose of Rubraca [see Use in Specific Populations (8.1) and Nonclinical Toxicology (13.1)].

8.4 Pediatric Use

The safety and effectiveness of Rubraca in pediatric patients have not been established.

8.5 Geriatric Use

Of the 937 patients with ovarian cancer who received Rubraca in ARIEL3, ARIEL2, and Study 10, 41% were age 65 or older and 10% were 75 years or older. No major differences in safety were observed between these patients and younger patients for the maintenance treatment of recurrent ovarian cancer or for the treatment of BRCA-mutated ovarian cancer after two or more chemotherapies.

8.6 Renal Impairment

No dosage modification is recommended for patients with mild to moderate renal impairment (creatinine clearance [CLcr] between 30 and 89 mL/min, as estimated by the Cockcroft-Gault method *[see Clinical Pharmacology (12.3)]*. Rubraca has not been studied in patients with CLcr $\leq$ 30 mL/min or patients on dialysis.

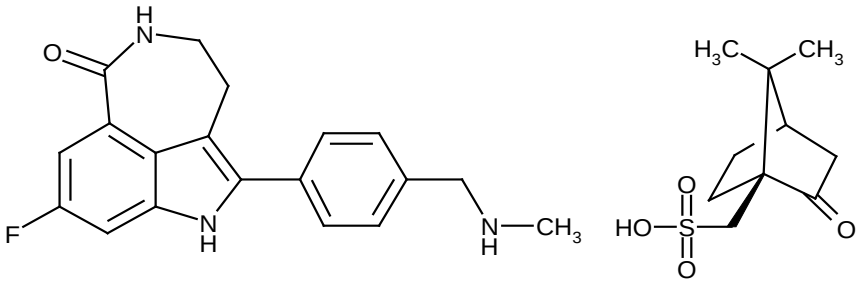
8.7 Hepatic Impairment

No dosage modification is recommended for patients with mild to moderate hepatic impairment (total bilirubin ≤ 3 x upper limit of normal [ULN] or AST > ULN) *[see Clinical Pharmacology (12.3)]*. Rubraca has not been studied in patients with severe hepatic impairment (total bilirubin > 3 x ULN and any AST).

11 DESCRIPTION

Rucaparib is an inhibitor of the mammalian polyadenosine 5'-diphosphoribose polymerase (PARP) enzyme. The chemical name is 8-fluoro-2-{4-[(methylamino)methyl]phenyl}-1,3,4,5-tetrahydro-6H-azepino[5,4,3-cd]indol-6-one ((1S,4R)-7,7-dimethyl-2-oxobicyclo[2.2.1]hept-1-yl)methanesulfonic acid salt. The chemical formula of rucaparib camsylate is $C_{19}H_{18}FN_3O \cdot C_{10}H_{16}O_4S$ and the relative molecular mass is 555.67 Daltons.

The chemical structure of rucaparib camsylate is shown below:



Rucaparib camsylate is a white to pale yellow powder; formulated into a tablet for oral use. Rucaparib shows pH-independent low solubility of approximately 1 mg/mL across the physiological pH range.

Rubraca (rucaparib) tablets contain rucaparib camsylate as the active ingredient. Each 200 mg tablet contains 344 mg rucaparib camsylate equivalent to 200 mg rucaparib free base. Each 250 mg tablet contains 430 mg rucaparib camsylate equivalent to 250 mg rucaparib free base. Each 300 mg tablet contains 516 mg rucaparib camsylate equivalent to 300 mg rucaparib free base.

The inactive ingredients in Rubraca tablets include: microcrystalline cellulose, sodium starch glycolate, colloidal silicon dioxide, and magnesium stearate. The cosmetic blue film coating for 200 mg tablets, cosmetic white film coating for 250 mg tablets, and cosmetic yellow film coating for 300 mg tablets is Opadry II containing polyvinyl alcohol, titanium dioxide, polyethylene glycol/macrogol, and talc. The coating is colorized as blue using brilliant blue aluminum lake and indigo carmine aluminum lake, or yellow using yellow iron oxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Rucaparib is an inhibitor of poly (ADP-ribose) polymerase (PARP) enzymes, including PARP-1, PARP-2, and PARP-3, which play a role in DNA repair. *In vitro* studies have shown that rucaparib-induced cytotoxicity may involve inhibition of PARP enzymatic activity and increased formation of PARP-DNA complexes resulting in DNA damage, apoptosis, and cancer cell death. Increased rucaparib-induced cytotoxicity and anti-tumor activity was observed in tumor cell lines with deficiencies in *BRCA1/2* and other DNA repair genes. Rucaparib has been shown to decrease tumor growth in mouse xenograft models of human cancer with or without deficiencies in *BRCA*.

12.2 Pharmacodynamics

The exposure-response relationship and time course of pharmacodynamic response for the safety and effectiveness of rucaparib has not fully been characterized.

Cardiac Electrophysiology

A positive concentration-QTc relationship was observedin patients who were administered continuous dosages of Rubraca ranging from 40 mg once daily (0.03 times the approved recommended dosage) to 840 mg twice daily (1.4 times the approved recommended dosage). The mean (90% confidence interval [CI]) QTcF increase from baseline at steady state of Rubraca 600 mgtwice daily was 14.9 msec (11.1, 18.7 msec).

12.3 Pharmacokinetics

The AUC and Cmax of rucaparib demonstrated linear pharmacokinetics over a dose range from 240 mg to 840 mg twice daily (0.4 times to 1.4 times the approved recommended dosage). The mean (coefficient of variation [CV]) steady-state rucaparib C_{max} is 1,940 ng/mL (54%) and AUC_{0-12h} is 16,900 h·ng/mL (54%) at the approved recommended dosage. The mean AUC accumulation ratio is 3.5 to 6.2 fold.

Absorption

The median T_{max} (min, max) at the steady state is 1.9 hours (0, 5.98) at the approved recommended dosage. The mean (min, max) absolute bioavailability is 36% (30%, 45%).

Effect of Food

Following a high-fat meal (approximately 800-1000 calories, including approximately 250 calories from carbohydrates, approximately 500-600 calories from fat, approximately 150 calories from protein), the C_{max} was increased by 20%, AUC_{0-24h} was increased by 38%, and the T_{max} was delayed by 2.5 hours, as compared to fasted conditions *[see Dosage and Administration (2.2)]*.

Distribution

The mean apparent volume of distribution is 2300 L (21%).

Rucaparib is 70% bound to human plasma proteins in vitro. Rucaparib preferentially distributed to red blood cells with a blood-to-plasma concentration ratio of 1.8.

Elimination

The mean apparent total clearance at steady state is 44.2 L/h (45%) and the mean terminal elimination half-life is 26 (39%) hours.

Metabolism

In vitro, rucaparib is primarily metabolized by CYP2D6 and to a lesser extent by CYP1A2 and CYP3A4. In addition to CYP-based oxidation, rucaparib also undergoes N-demethylation, N-methylation, and glucuronidation.

Excretion

Following a single oral dose of radiolabeled rucaparib, unchanged rucaparib accounted for 64% of the radioactivity. Rucaparib accounted for 45% and 95% of radioactivity in urine and feces, respectively.

Specific Populations

Age (20 to 86 years), race (White, Black and Asian), sex, body weight (41 to 171 kg), mild to moderate renal impairment (CLcr ≥ 30 mL/min), mild hepatic impairment (total bilirubin < ULN and AST > ULN or total bilirubin 1 to 1.5 x ULN and any AST), and CYP2D6 or CYP1A2 genotype polymorphisms did not have a clinically meaningful effect on the pharmacokinetics of rucaparib. The effect of severe renal impairment (CLcr 15 to 29 mL/min), end-stage renal disease (CLcr < 15 mL/min), or severe hepatic impairment (total bilirubin > 3 x ULN and any AST) has not been studied.*Hepatic Impairment*

Moderate hepatic impairment (total bilirubin > 1.5 to 3 x ULN and any AST) increased rucaparib AUC by 45%, but had no effect on Cmax compared to patients with normal hepatic function.

Drug Interaction Studies

Clinical Studies and Model-Informed Approaches

Effect of Other Drugs on Rucaparib

Concomitant administration of Rubraca with a proton pump inhibitor had no clinically meaningful effect on steady-state concentrations of rucaparib.

Effect of Rucaparib on Other Drugs

Concomitant administration of Rubraca with rosuvastatin (BCRP substrate) had no clinically meaningful effect on the concentrations of rosuvastatin.

Coadministration of Rubraca with the following substrates increased the C_{max} of each coadministered substrate by ≤ 1.1-fold and increased the AUC of each substrate as follows:

- Caffeine (CYP1A2): by 2.6-fold
- Midazolam (CYP3A4): by 1.4-fold
- Warfarin (CYP2C9): by 1.5-fold
- Omeprazole (CYP2C19): by 1.6-fold
- Digoxin (P-glycoprotein): by 1.2-fold

Concomitant administration of Rubraca with an oral contraceptive containing ethinylestradiol and levonorgestrel (CYP3A substrates): increased ethinylestradiol AUC by 1.4-fold and lenovorgestrel AUC by 1.6-fold, but did not have a clinically meaningful effect on their Cmax.

In Vitro Studies

Cytochrome P450 (CYP) Enzymes: Rucaparib inhibited CYP2C8, CYP2D6 and induced CYP1A2.

UDP-glucuronosyltransferase (UGT) Enzymes: Rucaparib inhibited UGT1A1.

Transporter Systems: Rucaparib is a substrate of P-gp and BCRP Rucaparib is not a substrate of OATP1B1, OATP1B3, OAT1, OAT3, or OCT2.

Rucaparib inhibited OATP1B1, OATP1B3, OAT1, OAT3, MATE1, MATE2-K, OCT1, OCT2, and MRP4. Rucaparib did not inhibit MRP2, MRP3, or BSEP.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with rucaparib.

Rucaparib was clastogenic in an *in vitro* chromosomal aberration assay in cultured human lymphocytes. The clastogenic response in mitotically-stimulated cells was anticipated based on the mechanism of action of rucaparib and indicates potential genotoxicity in humans. Rucaparib was not mutagenic in a bacterial reverse mutation (Ames) test.

Fertility studies with rucaparib have not been conducted. In 3-month repeat-dose general toxicology studies, rucaparib had no effects on male and female reproductive organs at doses up to 100 mg/kg/day and 20 mg/kg/day in rats and dogs,

respectively. These dose levels resulted in systemic exposures of approximately 0.3 and 0.09 times the human exposure ($AUC_{0\text{-}24h}$), respectively, at the recommended dose.

14 CLINICAL STUDIES

14.1 Maintenance Treatment of Recurrent Ovarian Cancer

The efficacy of Rubraca was investigated in ARIEL3 (NCT01968213), a double-blind, multicenter clinical trial in which 564 patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who were in response to platinum-based chemotherapy were randomized (2:1) to receive Rubraca tablets 600 mg orally twice daily (n=375) or placebo (n=189). Treatment was continued until disease progression or unacceptable toxicity. All patients had achieved a response (complete or partial) to their most recent platinum-based chemotherapy. Randomization was stratified by best response to last platinum (complete or partial), time to progression following the penultimate platinum therapy (6 to ≤ 12 months and > 12 months), and tumor biomarker status. The major efficacy outcome was investigator-assessed progression-free survival (PFS) evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1 (v1.1).

The median age was 61 years (range: 39 to 84) for patients receiving Rubraca and 62 years (range: 36 to 85) for those on placebo; the majority were White (80%); and 100% had an ECOG performance status of 0 or 1. All patients had received at least two prior platinum-based chemotherapies (range: 2 to 7). A total of 34% of patients were in complete response (CR) to their most recent therapy. The progression-free interval to penultimate platinum was 6-12 months in 40% of patients and > 12 months in 60%. Prior bevacizumab therapy was reported for 22% of patients who received Rubraca and 23% of patients who received placebo. Measurable disease was present at baseline in 37% of patients.

Tumor tissue samples were tested using a clinical trial assay (CTA) (N=564), and the FoundationFocus™ CDx $_{\text{BRCA LOH}}$ test (n=518). Of the samples evaluated with both tests, homologous recombination deficiency (HRD) positive status (as defined by the presence of a deleterious BRCA mutation or high genomic loss of heterozygosity) was confirmed by the FoundationFocus™ CDx $_{\text{BRCA LOH}}$ test for 94% (313/332) of HRD-positive patients determined by the CTA; and of these, tumor BRCA (tBRCA) mutant status was confirmed by the FoundationFocus™ CDx $_{\text{BRCA LOH}}$ test for 99% (177/178) of tBRCA-positive patients determined by the CTA. Blood samples for 94% (186/196) of the tBRCA patients were evaluated using a central blood germline BRCA test. Based on these results, 70% (130/186) of the tBRCA patients had a germline BRCA mutation and 30% (56/186) had a somatic BRCA mutation.

ARIEL3 demonstrated a statistically significant improvement in PFS for patients randomized to Rubraca as compared with placebo in all patients, and in the HRD and tBRCA subgroups. Results from a blinded independent radiology review were consistent. At the time of the analysis of PFS, overall survival (OS) data were not mature (with 22% of events).

Efficacy results are summarized in Table 6 and Figures 1, 2, and 3.

Table 6. Efficacy Results - ARIEL3 (Investigator Assessment)

	Rubraca	Placebo
All Patients[a]		
Patients, N	375	189
PFS events, n (%)	234 (62%)	167 (88%)
PFS, median in months	10.8	5.4
HR (95% CI)	0.36 (0.30, 0.45)	
p-value	< 0.0001	
HRD Group[b]		
Patients, N	236	118
PFS events, n (%)	134 (57%)	101 (86%)
PFS, median in months	13.6	5.4
HR (95% CI)	0.32 (0.24, 0.42)	
p-value	< 0.0001	
tBRCA Group[c]		
Patients, N	130	66
PFS events, n (%)	67 (52%)	56 (85%)
PFS, median in months	16.6	5.4
HR (95% CI)	0.23 (0.16, 0.34)	
p-value	< 0.0001	

a. All randomized patients.
b. HRD includes all patients with a deleterious germline or somatic BRCA mutation or high genomic loss of heterozygosity, as determined by the CTA.
c. tBRCA includes all patients with a deleterious germline or somatic BRCA mutation, as determined by the CTA.

Figure 1. Kaplan-Meier Curves of Progression-Free Survival in ARIEL3 as Assessed by Investigator: All Patients

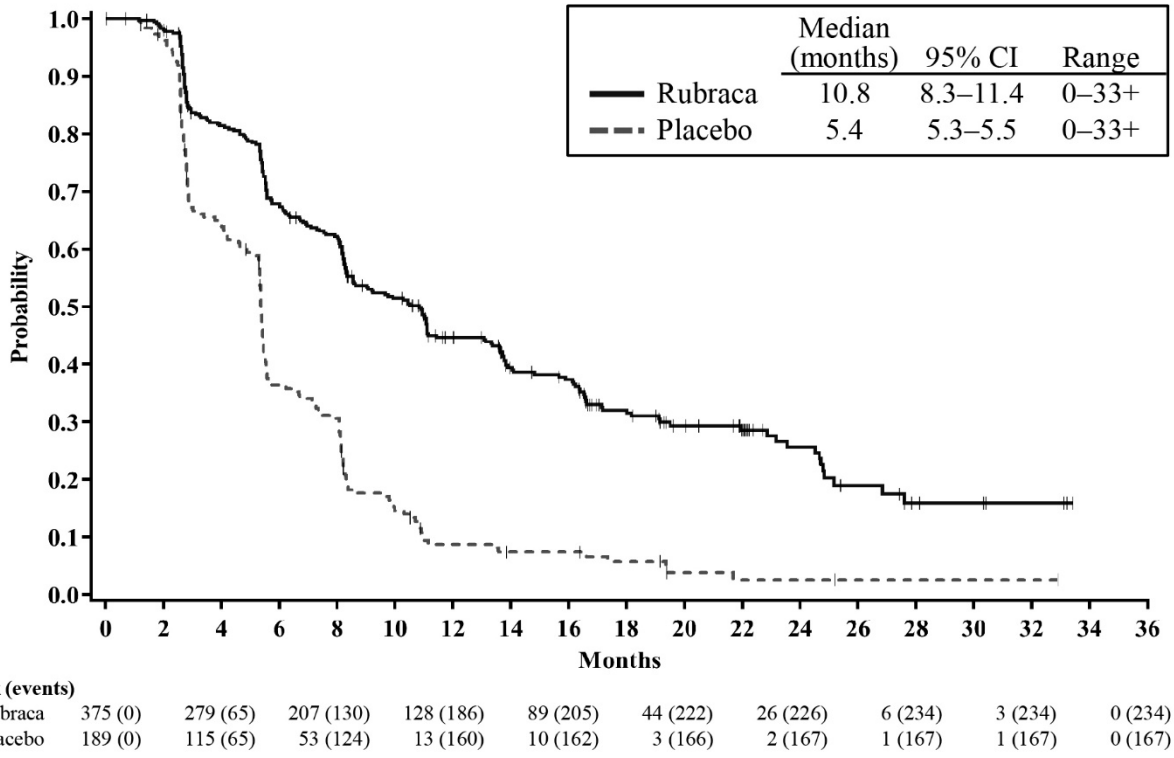
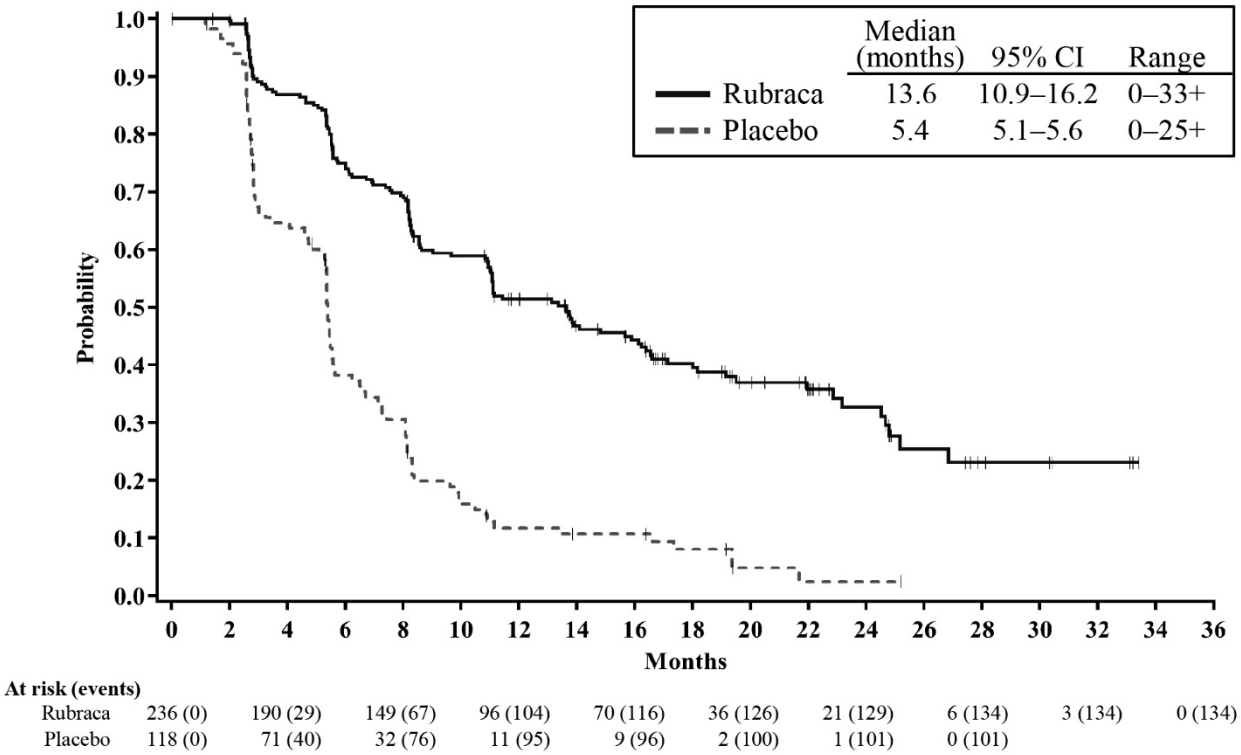


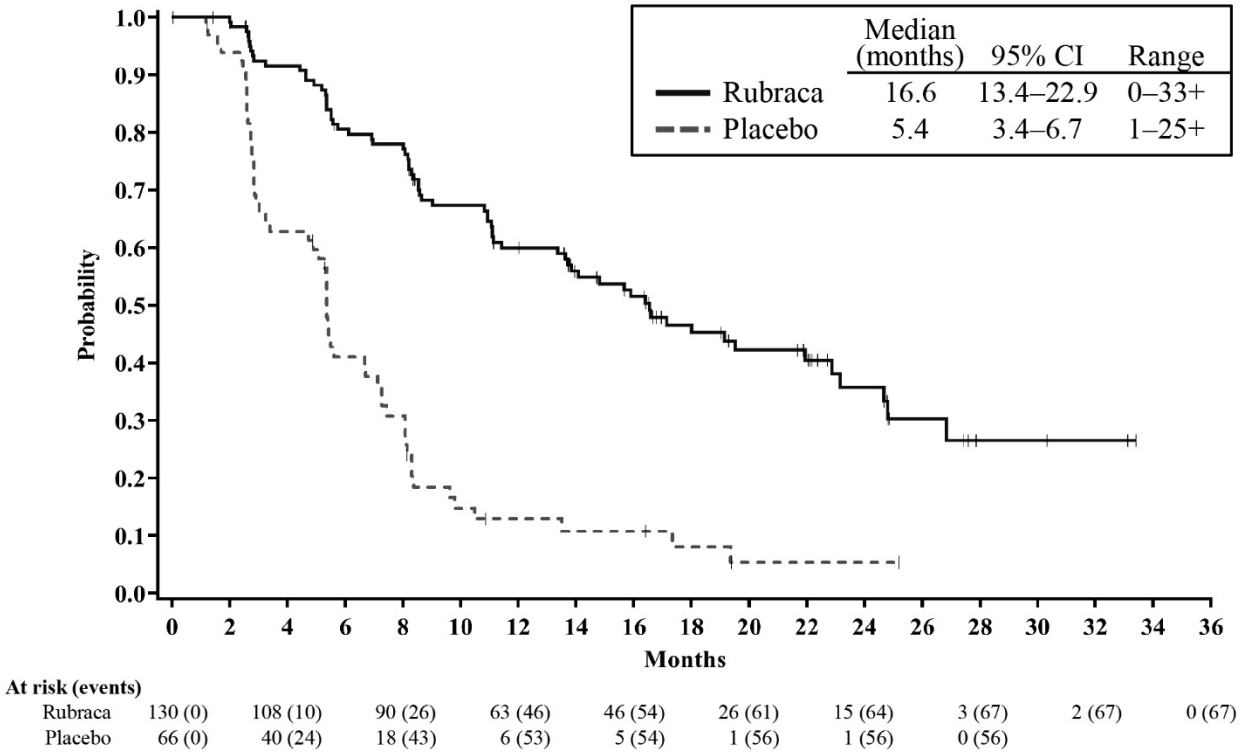
Figure 2. Kaplan-Meier Curves of Progression-Free Survival in ARIEL3 as Assessed by Investigator: HRD Group



At risk (events)

Rubraca	236 (0)	190 (29)	149 (67)	96 (104)	70 (116)	36 (126)	21 (129)	6 (134)	3 (134)	0 (134)
Placebo	118 (0)	71 (40)	32 (76)	11 (95)	9 (96)	2 (100)	1 (101)	0 (101)		

Figure 3. Kaplan-Meier Curves of Progression-Free Survival in ARIEL3 as Assessed by Investigator: tBRCA Group



At risk (events)

Rubraca	130 (0)	108 (10)	90 (26)	63 (46)	46 (54)	26 (61)	15 (64)	3 (67)	2 (67)	0 (67)
Placebo	66 (0)	40 (24)	18 (43)	6 (53)	5 (54)	1 (56)	1 (56)	0 (56)		

14.2 Treatment of BRCA-mutated Ovarian Cancer After 2 or More Chemotherapies

The efficacy of Rubraca was investigated in 106 patients in two multicenter, single-arm, open-label clinical trials, Study 10 (NCT01482715) and ARIEL2 (NCT01891344), in patients with advanced *BRCA*-mutant ovarian cancer who had progressed after 2 or more prior chemotherapies. All 106 patients received Rubraca 600 mg orally twice daily as monotherapy until disease progression or unacceptable toxicity. Objective response rate (ORR) and duration of response (DOR) were assessed by the investigator and IRR according to RECIST v1.1.

The median age of the patients was 59 years (range: 33 to 84), the majority were White (78%), and 100% had an ECOG performance status of 0 or 1. All patients had received at least two prior platinum-based chemotherapies and 43% had received 3 or more prior lines of platinum-based chemotherapy. There were 18/106 patients (17%) who had deleterious *BRCA* mutations detected in tumor tissue and not in whole blood specimens. Tumor *BRCA* mutation status was verified retrospectively in 96% (64/67) of the patients for whom a tumor tissue sample was available by the companion diagnostic FoundationFocus™ CDx$_{BRCA}$ test, which is FDA approved for selection of patients for Rubraca treatment.

Efficacy results are summarized in Table 7.

Table 7. Overall Response and Duration of Response in Patients with *BRCA*-mutant Ovarian Cancer Who Received 2 or More Chemotherapies in Study 10 and ARIEL2

	Investigator-assessed N=106
Objective Response Rate (95% CI)	54% (44, 64)
Complete Response	9%
Partial Response	45%
Median DOR in months (95% CI)	9.2 (6.6, 11.6)

Response assessment by independent radiology review was 42% (95% CI [32, 52]), with a median DOR of 6.7 months (95% CI [5.5, 11.1]). Investigator-assessed ORR was 66% (52/79; 95% CI [54, 76]) in platinum-sensitive patients, 25% (5/20; 95% CI [9, 49]) in platinum-resistant patients, and 0% (0/7; 95% CI [0, 41]) in platinum-refractory patients. ORR was similar for patients with a *BRCA1* gene mutation or *BRCA2* gene mutation.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

Rubraca is available as 200 mg, 250 mg, and 300 mg tablets.

200 mg Tablets:
- Blue, round, and debossed with “C2” on one side
- Supplied in bottles of 60 tablets

250 mg Tablets:
- White, diamond, and debossed with “C25” on one side
- Supplied in bottles of 60 tablets

300 mg Tablets:
- Yellow, oval, and debossed with “C3” on one side
- Supplied in bottles of 60 tablets

Storage

Store below 25°C.
Shelf life and storage after first opening: use for 30 days after opening. Store below 25°C.

Shelf life

The expiry date of the product is indicated on the packaging materials.

17 REGISTRATION NUMBER

RUBRACA 200 MG: 162-81-35664
RUBRACA 250 MG: 162-83-35666
RUBRACA 300 MG: 162-82-35665

18 REGISTRATION HOLDER

Neopharm Ltd.
Ha-Shiloah 6, Petach Tikva,
4917001, Israel

19 MANUFACTURER

Clovis Oncology, Inc.
Boulder, CO 80301, USA

Rubraca is a registered trademark of Clovis Oncology, Inc.

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