HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use RUBRACA safely and effectively. See full prescribing information for RUBRACA.

RUBRACA® (rucaparib) tablets, for oral use
Initial U.S. Approval: 2016

----------RECENT MAJOR CHANGES----------

Indications and Usage (1.1, 1.2)	04/2018
Dosing and Administration (2.3)	04/2018
Warnings and Precautions (5.1)	04/2018

----------INDICATIONS AND USAGE----------

RUBRACA is a poly (ADP-ribose) polymerase (PARP) inhibitor 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. (1.1)
- for the treatment of adult patients with 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. Select patients for therapy based on an FDA-approved companion diagnostic for RUBRACA. (1.2, 2.3)

----------DOSAGE AND ADMINISTRATION----------

- Recommended dose is 600 mg orally twice daily with or without food. (2.1)
- Continue treatment until disease progression or unacceptable toxicity. (2.1)
- For adverse reactions, consider interruption of treatment or dose reduction. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------

Tablets: 200 mg, 250 mg, and 300 mg (3)

----------CONTRAINDICATIONS----------

None. (4)

----------WARNINGS AND PRECAUTIONS----------

- Myelodysplastic Syndrome/Acute Myeloid Leukemia (MDS/AML): MDS/AML occurred in patients exposed to RUBRACA, and some cases were fatal. Monitor patients for hematological toxicity at baseline and monthly thereafter. Discontinue if MDS/AML is confirmed. (5.1)
- Embryo-Fetal Toxicity: RUBRACA can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception. (5.2, 8.1, 8.3)

----------ADVERSE REACTIONS----------

- Most common adverse reactions (≥ 20%) were nausea, fatigue (including asthenia), vomiting, anemia, dysgeusia, AST/ALT elevation, constipation, decreased appetite, diarrhea, thrombocytopenia, neutropenia, stomatitis, nasopharyngitis/URI, rash, abdominal pain/distention, and dyspnea (6.1)
- Most common laboratory abnormalities (≥ 25%) were increase in creatinine, increase in ALT, increase in AST, increase in alkaline phosphatase, decrease in hemoglobin, increase in cholesterol, decrease in platelets, decrease in leukocytes, decrease in lymphocytes, and decrease in neutrophils. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Clovis Oncology, Inc. at 1-844-258-7662 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- CYP1A2, CYP3A, CYP2C9, and CYP2C19 substrates: Adjust dosage if clinically indicated. (7)

----------USE IN SPECIFIC POPULATIONS----------

- Lactation: Advise women not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 04/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

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 *[see Dosage and Administration (2.1)]*.

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

Rubraca is indicated for the treatment of adult patients with 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. Select patients for therapy based on an FDA-approved companion diagnostic for Rubraca *[see Dosage and Administration (2.1)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose

The recommended dose of Rubraca is 600 mg (two 300 mg tablets) taken orally twice daily with or without food.

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.

2.2 Dose Modifications for Adverse Reactions

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

Table 1. Recommended Dose Adjustments

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)

2.3 Patient 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)]*. Information on the FDA-approved test for the detection of a tumor *BRCA* mutation in patients with ovarian cancer is available at: http://www.fda.gov/CompanionDiagnostics.

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

None.

5 WARNINGS AND PRECAUTIONS

5.1 Myelodysplastic Syndrome/Acute Myeloid Leukemia

Myelodysplastic Syndrome (MDS)/Acute Myeloid Leukemia (AML) occur uncommonly in patients treated with Rubraca, and are potentially fatal adverse reactions. In approximately 1100 treated patients, MDS/AML occurred in 12 patients (1.1%), including those in long term follow-up. Of these, 5 occurred during treatment or during the 28 day safety follow-up (0.5%). The duration of Rubraca treatment prior to the diagnosis of MDS/AML ranged from 1 month to approximately 28 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.

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 (2.2)]* 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)]*.

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)]*.

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.

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

	Rubraca N=372		**Placebo N=189**	
Adverse reactions	**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

	Rubraca N=372		Placebo N=189	
Laboratory Parameter[a]	**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. 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. Adverse Reactions Reported in ≥ 20% of Patients with Ovarian Cancer After ≥ 2 Chemotherapies Treated with Rubraca in Study 10 and ARIEL2

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%), 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 ARIEL2

Laboratory Parameter	All Patients with Ovarian Cancer (N = 377) %	
	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 Rucaparib on Cytochrome p450 (CYP) Substrates

Co-administration of rucaparib can increase the systemic exposure of CYP1A2, CYP3A, CYP2C9, or CYP2C19 substrates *[see Clinical Pharmacology (12.3)]*, which may increase the risk of toxicities of these drugs.

Adjust dosage of CYP1A2, CYP3A, CYP2C9, or CYP2C19 substrates, if clinically indicated. If co-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.

The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

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

Pregnancy Testing

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

Contraception

Females

Rubraca can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*. Advise females of reproductive potential to use effective contraception during treatment and for 6 months following the last dose of Rubraca.

8.4 Pediatric Use

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

8.5 Geriatric Use

In clinical studies 40% (297/749) of patients with ovarian cancer treated with Rubraca were 65 years of age or older and 9% (65/749) were 75 years or older. Grade 3-4 adverse reactions occurred in 65% of patients 65 years or older and in 63% of patients 75 years or older. For patients 65 years or older, the most common Grade 3-4 adverse reactions were anemia, fatigue/asthenia, and ALT/AST increase. 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 Hepatic Impairment

No starting dose adjustment is recommended for patients with mild hepatic impairment (total bilirubin less than or equal to upper limit of normal [ULN] and AST greater than ULN, or total bilirubin between 1.0 to 1.5 times ULN and any AST). No recommendation for starting dose adjustment is available for patients with moderate to severe hepatic impairment (total bilirubin greater than 1.5 times ULN) due to a lack of data *[See Clinical Pharmacology (12.3)]*.

8.7 Renal Impairment

No starting dose adjustment is recommended for patients with mild to moderate renal impairment (baseline creatinine clearance [CLcr] between 30 and 89 mL/min, as estimated by the Cockcroft-Gault method). There is no recommended starting dose for patients with CLcr less than 30 mL/min or patients on dialysis due to a lack of data *[See Clinical Pharmacology (12.3)]*.

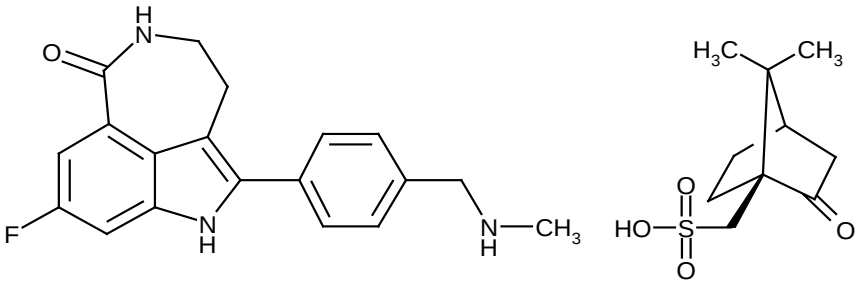
10 OVERDOSAGE

There is no specific treatment in the event of Rubraca overdose, and symptoms of overdose are not established. In the event of suspected overdose, physicians should follow general supportive measures and should treat symptomatically.

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 pharmacodynamic response of rucaparib has not been characterized.

Cardiac Electrophysiology

The effect of multiple doses of Rubraca on QTc interval was evaluated in an open-label single-arm study in 56 patients with solid tumors who were administered continuous doses of Rubraca ranging from 40 mg once daily (0.03 times the approved recommended dose) to 840 mg twice daily (1.4 times the approved recommended dose). The mean QTcF increase from baseline (90% confidence interval [CI]) in population pharmacokinetics estimated 95th percentile C_{max} (3019 ng/mL) at steady state of 600 mg rucaparib twice daily was 14.9 msec (11.1-18.7 msec).

12.3 Pharmacokinetics

The pharmacokinetic profile of rucaparib was characterized in patients with cancer. Rucaparib demonstrated linear pharmacokinetics over a dose range from 240 to 840 mg twice daily with time-independence and dose-proportionality. The mean steady-state rucaparib C_{max} was 1940 ng/mL (54% coefficient of variation [CV]) and $AUC_{0\text{-}12h}$ was 16900 h·ng/mL (54% CV) at the approved recommended dose. Accumulation was 3.5 to 6.2 fold.

Absorption

The median T_{max} was 1.9 hours at the approved recommended dose. The mean absolute bioavailability of rucaparib immediate-release tablet was 36% with a range from 30% to 45%.

Following a high-fat meal, the C_{max} was increased by 20% and AUC_{0-24h} was increased by 38%, and T_{max} was delayed by 2.5 hours, as compared to dosing under fasted conditions *[see Dosage and Administration (2.2)]*.

Distribution

Rucaparib had a steady-state volume of distribution of 113 L to 262 L following a single intravenous dose of 12 mg to 40 mg rucaparib.

In vitro, the protein binding of rucaparib was 70% in human plasma at therapeutic concentrations. Rucaparib preferentially distributed to red blood cells with a blood-to-plasma concentration ratio of 1.83.

Elimination

The mean terminal $T_{1/2}$ of rucaparib was 17 to 19 hours, following a single oral dose of 600 mg rucaparib. The apparent clearance ranged from 15.3 to 79.2 L/hour, following rucaparib 600 mg twice daily. The clearance ranged from 13.9 to 18.4 L/hour, following a single intravenous dose of rucaparib 12 mg to 40 mg.

Metabolism

In vitro, rucaparib had a low metabolic turnover rate and was metabolized primarily by CYP2D6 and to a lesser extent by CYP1A2 and CYP3A4.

Specific Populations

Age, Race, and Body Weight

Based on population pharmacokinetic analyses, age, race, and body weight did not have a clinically meaningful effect on rucaparib exposure.

Renal Impairment

In patients who received Rubraca 600 mg twice daily, those with mild renal impairment (N=148; baseline CLcr between 60 and 89 mL/min, as estimated by the Cockcroft-Gault method) and those with moderate renal impairment (N=72; CLcr between 30 and 59 mL/min) showed approximately 15% and 32% higher steady-state AUC, respectively, compared to patients with normal renal function (N=143; CLcr greater than or equal to 90 mL/min). The pharmacokinetic characteristics of rucaparib in patients with CLcr less than 30 mL/min or patients on dialysis are unknown.

Hepatic Impairment

Based on population pharmacokinetic analyses, no apparent pharmacokinetic difference was observed in 34 patients with mild hepatic impairment (total bilirubin less than or equal to ULN and AST greater than ULN, or total bilirubin between 1.0 to 1.5 times ULN and any AST) who received Rubraca 600 mg twice daily as compared to patients with normal hepatic function (N=337). The pharmacokinetic characteristics of rucaparib in patients with moderate to severe hepatic impairment (total bilirubin greater than 1.5 times ULN) are unknown.

CYP Enzyme Polymorphism

Based on population pharmacokinetic analyses, steady-state concentrations following rucaparib 600 mg twice daily did not differ significantly across CYP2D6 or CYP1A2 genotype subgroups.

Drug Interaction Studies

Effect of Rucaparib on Other Drugs

Clinical Studies

A single dose of the following drugs was administered before and following rucaparib 600 mg twice daily for 7 days. The C_{max} of each co-administered drug was ≤ 1.13-fold, and the AUC changed as follows:

- Caffeine (CYP1A2): caffeine AUC increased by 2.55-fold
- Midazolam (CYP3A4): midazolam AUC increased by 1.38-fold
- Warfarin (CYP2C9): warfarin AUC increased by 1.49-fold
- Omeprazole (CYP2C19): omeprazole AUC increased by 1.55-fold
- Digoxin (P-glycoprotein): digoxin AUC increased by 1.20-fold

In Vitro Studies

Rucaparib inhibited CYP2C8, CYP2D6, and uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1). Rucaparib induced CYP1A2, and down regulated CYP3A4 and CYP2B6.

Rucaparib inhibited the P-glycoprotein (P-gp) efflux transporter, breast cancer resistance protein (BCRP), organic anion transporting polypeptides 1B1 and 1B3 (OATP1B1 and OATP1B3), organic anion transporters 1 and 3 (OAT1 and OAT3), multidrug and toxin extrusion 1 and 2-k (MATE1 and MATE2-K), organic cation transporters 1 and 2 (OCT1 and OCT2), and multidrug resistance-associated protein 4 (MRP4). No apparent inhibition was observed for MRP2, MRP3, or BSEP.

Effects of Other Drugs on Rucaparib

Clinical Studies

In a population pharmacokinetic (PPK) analysis, co-administration with proton pump inhibitors had no clinically significant effect on steady-state concentrations of rucaparib.

In Vitro Studies

Rucaparib was a substrate of P-gp and BCRP; however, rucaparib was not a substrate of OATP1B1, OATP1B3, OAT1, OAT3, and OCT2.

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).

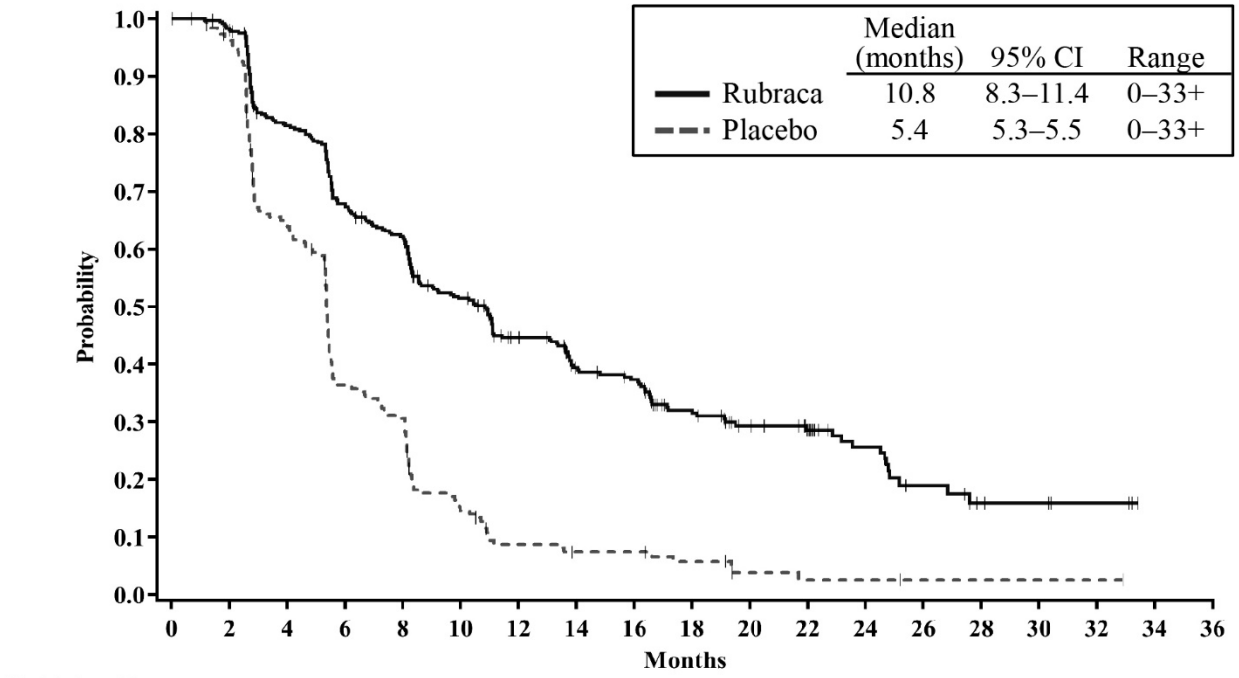
Efficacy results are summarized in Table 6 and Figures 1, 2, and 3.

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.

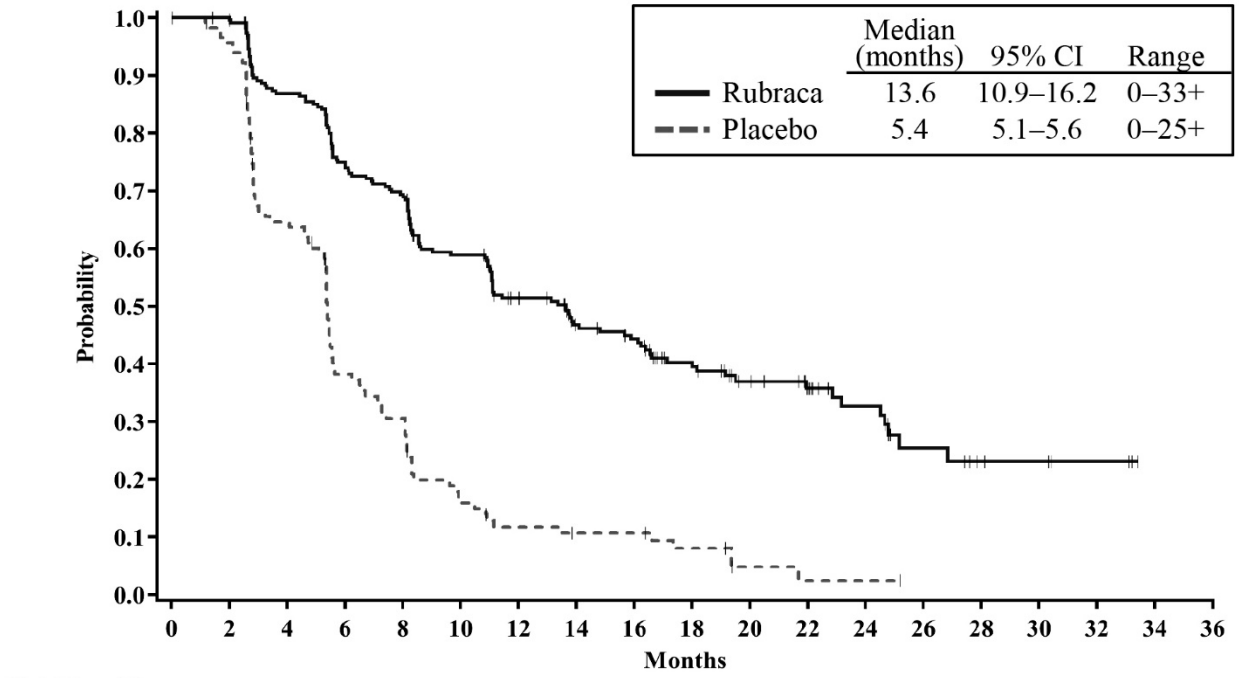
Figure 1. Kaplan-Meier Curves of Progression-Free Survival in ARIEL3 as Assessed by Investigator: All Patients



At risk (events)

Rubraca	375 (0)	279 (65)	207 (130)	128 (186)	89 (205)	44 (222)	26 (226)	6 (234)	3 (234)	0 (234)
Placebo	189 (0)	115 (65)	53 (124)	13 (160)	10 (162)	3 (166)	2 (167)	1 (167)	1 (167)	0 (167)

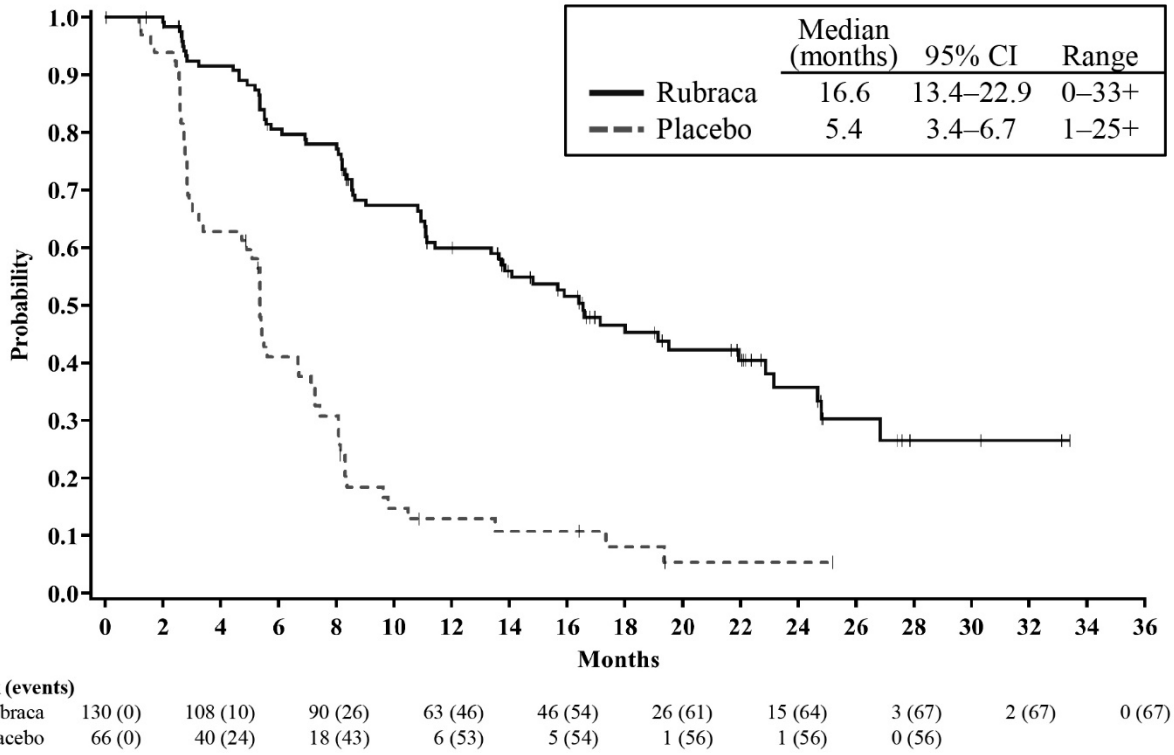
Figure 2. Kaplan-Meier Curves of Progression-Free Survival in ARIEL3 as Assessed by Investigator: HRD Group



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



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

16.1 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 (NDC: 69660-201-91)

250 mg Tablets:
- White, diamond, and debossed with “C25” on one side
- Supplied in bottles of 60 tablets (NDC: 69660-202-91)

300 mg Tablets:
- Yellow, oval, and debossed with “C3” on one side
- Supplied in bottles of 60 tablets (NDC: 69660-203-91)

16.2 Storage

Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [*see USP Controlled Room Temperature*].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

MDS/AML: Advise patients to contact their healthcare provider if they experience weakness, feeling tired, fever, weight loss, frequent infections, bruising, bleeding easily, breathlessness, blood in urine or stool, and/or laboratory findings of low blood cell counts, or a need for blood transfusions. These may be signs of hematological toxicity or a more serious uncommon bone marrow problem called ‘myelodysplastic syndrome’ (MDS) or ‘acute myeloid leukemia’ (AML) which have been reported in patients treated with Rubraca *[see Warnings and Precautions (5.1)]*.

Embryo-Fetal Toxicity: Advise females to inform their healthcare provider if they are pregnant or become pregnant. Inform female patients of the risk to a fetus and potential loss of the pregnancy *[see Use in Specific Populations (8.1)]*. Advise females of reproductive potential to use effective contraception during treatment and for 6 months after receiving the last dose of Rubraca *[see Warnings and Precautions (5.2) and Use in Specific Populations (8.1, 8.3)]*.

Photosensitivity: Advise patients to use appropriate sun protection due to the increased susceptibility to sunburn while taking Rubraca *[see Adverse Drug Reactions (6.1)]*.

Lactation: Advise females not to breastfeed during treatment and for 2 weeks after the last dose of Rubraca *[see Use in Specific Populations (8.2)]*.

Dosing Instructions: Instruct patients to take Rubraca orally twice daily with or without food. Doses should be taken approximately 12 hours apart. Advise patients that if a dose of Rubraca is missed or if the patient vomits after taking a dose of Rubraca, patients should not take an extra dose, but take the next dose at the regular time *[see Dosage and Administration (2.1)]*.

Distributed by:
Clovis Oncology, Inc.
Boulder, CO 80301
1-844-258-7662

PATIENT INFORMATION
Rubraca® (roo-brah'-kah)
(rucaparib)
Tablets

What is the most important information I should know about Rubraca?

Rubraca may cause serious side effects including:

Bone marrow problems called Myelodysplastic Syndrome (MDS) or a type of cancer of the blood called Acute Myeloid Leukemia (AML). Some people who have cancer and who have received previous treatment with chemotherapy or certain other medicines for their cancer have developed MDS or AML during or after treatment with Rubraca. MDS or AML may lead to death. If you develop MDS or AML, your healthcare provider will stop treatment with Rubraca.

Symptoms of low blood cell counts are common during treatment with Rubraca, but can be a sign of serious problems, including MDS or AML. Tell your healthcare provider if you have any of the following symptoms during treatment with Rubraca:

- weakness
- weight loss
- fever
- frequent infections
- blood in urine or stool
- shortness of breath
- feeling very tired
- bruising or bleeding more easily

Your healthcare provider will do blood tests to check your blood cell counts:

- before treatment with Rubraca.
- every month during treatment with Rubraca.
- weekly if you have low blood cell counts for a long time. Your healthcare provider may stop treatment with Rubraca until your blood cell counts improve.

See "What are possible side effects of Rubraca?" for more information about side effects.

What is Rubraca?

Rubraca is a prescription medicine used for:

- the maintenance treatment of adults with ovarian cancer, fallopian tube cancer, or primary peritoneal cancer whose cancer has come back and who are in response (complete or partial response) to a platinum-based chemotherapy.
- the treatment of adults with ovarian cancer, fallopian tube cancer, or primary peritoneal cancer who have certain "*BRCA*" gene mutations, either inherited (germline) or acquired (somatic), and who have been treated with 2 or more chemotherapy medicines for their cancer.

  Your healthcare provider will perform a test to make sure Rubraca is right for you.

It is not known if Rubraca is safe and effective in children.

Before you take Rubraca, tell your healthcare provider about all of your medical conditions, including if you:

- are pregnant or plan to become pregnant. Rubraca can harm your unborn baby and may cause loss of pregnancy (miscarriage). You should not become pregnant during treatment with Rubraca.
  - If you are able to become pregnant, your healthcare provider may do a pregnancy test before you start treatment with Rubraca.
  - Females who are able to become pregnant should use effective birth control during treatment and for 6 months after the last dose of Rubraca. Talk to your healthcare provider about birth control methods that may be right for you.
  - Tell your healthcare provider right away if you become pregnant.
- are breastfeeding or plan to breastfeed. It is not known if Rubraca passes into breast milk. Do not breastfeed during treatment and for 2 weeks after the last dose of Rubraca. Talk to your healthcare provider about the best way to feed your baby during this time.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How should I take Rubraca?

- Take Rubraca exactly as your healthcare provider tells you.
- Your healthcare provider may temporarily stop treatment with Rubraca or change your dose of Rubraca if you have side effects. Do not change your dose or stop taking Rubraca unless your healthcare provider tells you to.
- Take Rubraca 2 times a day. Each dose should be taken about 12 hours apart.
- Take Rubraca with or without food.

- If you miss a dose of Rubraca, take your next dose at your usual scheduled time. Do not take an extra dose to make up for a missed dose.
- If you vomit after taking a dose of Rubraca, do not take an extra dose. Take your next dose at your usual time.
- If you take too much Rubraca, call your healthcare provider or go to the nearest emergency room right away.

What should I avoid while taking Rubraca?

Avoid spending time in sunlight. Rubraca can make your skin sensitive to the sun (photosensitivity). You may sunburn more easily during treatment with Rubraca. You should wear a hat and clothes that cover your skin and use sunscreen to help protect against sunburn if you have to be in the sunlight.

What are the possible side effects of Rubraca?

Rubraca may cause serious side effects.

- **See "What is the most important information I should know about Rubraca?"**

The most common side effects of Rubraca include:

- nausea
- tiredness or weakness
- vomiting
- decrease in hemoglobin (anemia)
- changes in how food tastes
- constipation
- decreased appetite
- diarrhea
- low blood cell counts
- mouth sores
- upper respiratory tract infection
- shortness of breath
- rash
- changes in liver or kidney function blood tests
- stomach (abdomen) pain
- increased cholesterol levels

These are not all of the possible side effects of Rubraca. For more information, ask your healthcare provider or pharmacist.

Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store Rubraca?

- Store Rubraca at room temperature between 68°F to 77°F (20°C to 25°C).

Keep Rubraca and all medicines out of the reach of children.

General information about the safe and effective use of Rubraca

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use Rubraca for a condition for which it was not prescribed. Do not give it to other people, even if they have the same symptoms you have. It may harm them. You can ask your healthcare provider or pharmacist for more information about Rubraca.

What are the ingredients in Rubraca?

Active ingredient: rucaparib

Inactive ingredients: microcrystalline cellulose, sodium starch glycolate, colloidal silicon dioxide, and magnesium stearate. The film coating contains polyvinyl alcohol, titanium dioxide, polyethylene glycol/macrogol, and talc. The blue film coating contains brilliant blue aluminum lake and indigo carmine aluminum lake. The yellow film coating contains yellow iron oxide.

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For more information, go to www.Rubraca.com or call 1-844-258-7662.

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: April 2018