

# Prescription Form



## Simple steps to getting Rubraca

You can send your patient's Rubraca prescription to either your practice's in-office dispensing (IOD) pharmacy or one of our Rubraca network specialty pharmacies. A Rubraca Connections Access Specialist is available, if needed, to help determine eligibility and coordinate the financial assistance process, and answer any questions you may have.

### IOD PHARMACY

### SPECIALTY PHARMACY

- 1 Submit a Rubraca prescription to your practice's IOD pharmacy via fax or online at [RubracaConnections.com/iAssist](http://RubracaConnections.com/iAssist).
- 2 Your IOD pharmacy can order Rubraca directly from one of our wholesalers. If your IOD pharmacy is not in-network, the pharmacist will forward to a network specialty pharmacy. Rubraca Connections can also assist with the triage process.



Complete a Rubraca prescription and send to a network specialty pharmacy via fax or online at [RubracaConnections.com/iAssist](http://RubracaConnections.com/iAssist).

If you would like assistance identifying a network specialty pharmacy accepted by your patient's insurance, contact Rubraca Connections.

#### Avella

Phone: 877-546-5779 | Fax: 877-546-5780

#### Biologics

Phone: 800-850-4306 | Fax: 800-823-4506

#### CVS Specialty

Phone: 800-259-1783 | Fax: 855-296-0210

#### US Bioservices

Phone: 877-757-0667 | Fax: 888-899-0067

The specialty pharmacy will coordinate with Rubraca Connections if financial support is required.



For further financial or reimbursement support for your patients, contact Rubraca Connections



Call **1-844-779-7707**  
Monday through Friday 8 AM to 8 PM ET



Fax **1-844-779-7717**



Visit **RubracaConnections.com**

# Prescription Form – Patient



## A PATIENT AND CAREGIVER INFORMATION

Patient name (first and last) \_\_\_\_\_ Date of birth \_\_\_\_\_ Gender  M  F  
Address \_\_\_\_\_ City \_\_\_\_\_ State \_\_\_\_\_ ZIP \_\_\_\_\_  
Home phone \_\_\_\_\_ Cell phone \_\_\_\_\_ E-mail \_\_\_\_\_  
Social Security number \_\_\_\_\_ Language assistance required? Yes (please specify language) \_\_\_\_\_ No  
Caregiver name (first and last) \_\_\_\_\_ Caregiver phone \_\_\_\_\_

## B INSURANCE INFORMATION – Fill out or attach legible front/back copy of pharmacy benefit card.

Primary insurance \_\_\_\_\_ Insurance company phone \_\_\_\_\_  
Health plan policy # \_\_\_\_\_ Group # \_\_\_\_\_ No insurance  
Primary card holder \_\_\_\_\_ Primary card holder date of birth \_\_\_\_\_  
Relationship to card holder  Self  Other (please specify) \_\_\_\_\_  
.....  
Prescription benefit insurance \_\_\_\_\_ Prescription benefit insurance phone \_\_\_\_\_  
Primary card holder \_\_\_\_\_ Primary card holder date of birth \_\_\_\_\_  
Relationship to card holder  Self  Other (please specify) \_\_\_\_\_  
Would you like Rubraca Connections to contact your patient with an explanation of benefits?  Yes  No  
*Note: Your patient may be contacted about delivery of Rubraca® (rucaparib) tablets.*

## C RUBRACA CONNECTIONS PATIENT ASSISTANCE PROGRAM – If patient is uninsured or rendered uninsured and would like to apply for the Rubraca Connections Patient Assistance Program, please complete below. Patient application may be subject to audit or request for additional information. **Please also complete the Rubraca Connections Patient Assistance Program checklist on page 4.**

Yearly gross household income \_\_\_\_\_ Household size (number of people who contribute to or are dependent on your household income) \_\_\_\_\_  
Rubraca Connections policy prohibits prescribers from charging the patient any fee for enrollment or other activities associated with the patient's participation in the Rubraca Connections Patient Assistance Program. No claim may be made to any third-party payer: eg, Medicaid, Medicare, private insurance, etc.) for payment for product provided under the Rubraca Connections Patient Assistance Program. No purchase is necessary. Product may not be used for resale, returned for credit, or shared with other patients. Clovis reserves the right to rescind, revoke, or change the program at any time without notice. Visit RubracaConnections.com for complete Terms and Conditions and eligibility criteria.  
*Note: If patient does not provide signature below, consent will be acquired at a later stage for enrollment in the Rubraca Connections Patient Assistance Program.*

## D PATIENT PROGRAM CONSENT

I authorize my healthcare providers, health plans and pharmacies (collectively, "Healthcare Organizations") to use and share my personal and health information related to my medical condition and drug therapy ( my "health information") with Clovis Oncology and its patient support programs (collectively, "Rubraca Connections") (i) for reimbursement assistance, (ii) for referral to and enrollment in patient support and/or financial assistance programs, (iii) for providing me with materials and information about my treatment or other programs related to my drug therapy and enrolling me in such programs as I request, (iv) to contact me for market research purposes about Rubraca and Rubraca Connections, (v) to improve Rubraca Connections quality of operations, or (vi) as required or permitted by law. I understand that, once disclosed pursuant to this authorization, my health information may no longer be protected under federal or state law and could be disclosed by Rubraca Connections to others, but I understand that Rubraca Connections will make reasonable efforts to keep it private and to disclose it only for the purposes set forth in this authorization. I understand that my pharmacy may receive payment from Clovis Oncology in connection with (i) the disclosure of my health information to Rubraca Connections for purposes allowed under this authorization, including but not limited to market research purposes and (ii) the use of my health information to communicate with me about Clovis Oncology products or services. I understand that my authorization is voluntary and my healthcare providers, health plans and pharmacies may not condition my treatment, payment for treatment, enrollment or eligibility for benefits on whether I sign this authorization. However, if I do not sign this authorization, it may affect my ability to enroll in Rubraca Connections. I understand that this authorization will remain valid for 5 years after the date of my signature or such earlier date as required by applicable law, unless I revoke it earlier by cancelling my enrollment, which I may do by writing to PO Box 220308, Charlotte, NC 28222-0308 at any time. I understand that my cancellation will not apply to any use or disclosure of my health information by my healthcare providers, health plans or pharmacies before they receive notice of my cancellation. I certify that I will not seek reimbursement or credit for this prescription from any insurer, health plan, or government program, including Medicare and Medicaid.

**Patient signature**  \_\_\_\_\_ Date \_\_\_\_\_

Print patient first and last name \_\_\_\_\_

Print legal representative first and last name (If patient is unable to sign) \_\_\_\_\_

*If signed by someone other than the patient, please describe your legal authority/power of attorney to sign on behalf of the patient (eg, guardian, custodian, healthcare power of attorney). Please note that if you are the patient's prescriber, that alone does not give you legal authority to sign on behalf of the patient.*

## E PRESCRIBER INFORMATION

Prescriber name \_\_\_\_\_ Prescriber specialty \_\_\_\_\_  
 Practice/facility name \_\_\_\_\_  
 DEA/NPI prescriber license # \_\_\_\_\_ Medicaid/Medicare provider # \_\_\_\_\_  
 Address \_\_\_\_\_ City \_\_\_\_\_ State \_\_\_\_\_ ZIP \_\_\_\_\_  
 Office contact \_\_\_\_\_ Preferred communication method \_\_\_\_\_ Phone \_\_\_\_\_ Fax \_\_\_\_\_ E-mail \_\_\_\_\_  
 Phone \_\_\_\_\_ Fax \_\_\_\_\_ E-mail \_\_\_\_\_

## F DIAGNOSIS AND PRESCRIPTION – Complete the Rubraca® (rucaparib) tablets prescription in the space provided below or attach separately.

Patient name (first and last) \_\_\_\_\_ Date of birth \_\_\_\_\_

ICD-10 \_\_\_\_\_ Diagnosis \_\_\_\_\_

Drug: Rubraca    Dosage    200 mg    250 mg    300 mg    Days' supply    15 days    30 days    Quantity \_\_\_\_\_ Refills \_\_\_\_\_

Directions for use \_\_\_\_\_

*The recommended starting dose and schedule for Rubraca is 600 mg taken twice daily. If your patient misses a dose of Rubraca, instruct them to take their next dose at their usual scheduled time. Your patient should not take an extra dose to make up for a missed dose.*

Medication needed-by date \_\_\_\_\_

**Prescriber signature X** \_\_\_\_\_ Date \_\_\_\_\_

I have determined that Rubraca is medically appropriate for the treatment of the patient, and authorize Rubraca Connections to convey the attached prescription on my behalf to the selected specialty pharmacy and to receive information on the status and related matters.

## G QUICKSTART PRESCRIPTION – Complete for patients who experience an insurance delay of 5 business days or more.

Patients with private/commercial or government insurance receive 15-day supplies of Rubraca for up to 60 days (2 months) during insurance coverage investigations. Patients must meet diagnosis and coverage criteria to be eligible. Visit RubracaConnections.com for complete Terms and Conditions and eligibility criteria.

Patient name (first and last) \_\_\_\_\_ Date of birth \_\_\_\_\_

Drug: Rubraca    Dosage    200 mg    250 mg    300 mg    Days' supply 15    Quantity \_\_\_\_\_ Refills (3 max) \_\_\_\_\_

Directions for use \_\_\_\_\_

*The recommended starting dose and schedule for Rubraca is 600 mg taken twice daily. If your patient misses a dose of Rubraca, instruct them to take their next dose at their usual scheduled time. Your patient should not take an extra dose to make up for a missed dose.*

Medication needed-by date \_\_\_\_\_

**Prescriber signature X** \_\_\_\_\_ Date \_\_\_\_\_

I have determined that Rubraca is medically appropriate for the treatment of the patient.

## H DELIVERY – Choose one of the following options for ordering Rubraca.

Specialty pharmacy (select one) – If you have a question about selecting a specialty pharmacy, please contact Rubraca Connections at 1-844-779-7707.

Avella (Fax: 877-546-5780)   
  Biologics (Fax: 800-823-4506)   
  CVS Specialty (Fax: 855-296-0210)   
  US Bioservices (Fax: 888-899-0067)

OR

Your in-office dispensing (IOD) pharmacy (name) \_\_\_\_\_ Phone \_\_\_\_\_

Preferred shipment location    Prescriber office    Patient home

**Please see Select Important Safety Information on pages 5 and 6. Please see accompanying Prescribing Information for additional Important Safety Information.**

# Rubraca Prescription Form checklist



Required fields populated

Refer to the checklist below depending on your preferred delivery method:

## IOD pharmacy

- ✓ Sections A, B, D, E, and H are always required
- ✓ If submitting the form as a prescription, please complete section F
- ✓ If you would like to enroll a patient in the Rubraca Connections QuickStart Program, please complete section G
- ✓ If you would like to determine a patient's eligibility to apply to the Rubraca Connections Patient Assistance Program, please complete section C

## Specialty pharmacy

- ✓ Sections A, B, D, E, F, and H are always required
- ✓ If you would like to enroll a patient in the Rubraca Connections QuickStart Program, please complete section G
- ✓ If you would like to determine a patient's eligibility to apply to the Rubraca Connections Patient Assistance Program, please complete section C

Signatures obtained

- ✓ From healthcare provider  
*Required if using the form as a prescription or if enrolling a patient in the Rubraca Connections QuickStart Program*
- ✓ From patient  
*Recommended but not required in order to receive access support*

Pharmacy benefit card attached

## Rubraca Connections Patient Assistance Program checklist

For proof of household income, please include **one of the following**:

- ✓ A copy of last year's federal income tax returns for the patient, and the patient's spouse and dependents
- ✓ All income statements from jobs last year (W-2 or 1099)
- ✓ Two current pay stubs
- ✓ Current Social Security income yearly benefits statement

and

If your patient is a Medicare Part D enrollee, please also include **one of the following** (demonstrating at least 3% of the patient's income spent on prescription drugs in the calendar year):

- ✓ A copy of the patient's Medicare Part D Prescription Drug Plan statement (Explanation of Benefits [EOB])
- ✓ A summary document from the patient's pharmacy indicating the amount spent for prescriptions in the current calendar year

Free drug to Medicare Part D patients is provided outside of the Medicare Part D benefit. Patients may not seek reimbursement from their Part D plan or any other insurer for the free product they receive through the Rubraca Patient Assistance Program (PAP). Free product received will not count toward the patient's Medicare true-out-of-pocket (TrOOP) expenses for prescription drugs.

## Indications

### Maintenance:

Rubraca<sup>®</sup> (rucaparib) tablets are 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.

### Treatment:

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.

## Select Important Safety Information

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 regimens and/or other DNA damaging agents.

Do not start Rubraca until patients have recovered from hematological toxicity caused by previous chemotherapy ( $\leq$  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 (see Dosage and Administration (2.2) in full Prescribing Information) 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.

Based on its mechanism of action and findings from animal studies, Rubraca can cause fetal harm when administered to a pregnant woman. 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.

Most common adverse reactions in ARIEL3 ( $\geq$  20%; Grade 1-4) were nausea (76%), fatigue/asthenia (73%), abdominal pain/distention (46%), rash (43%), dysgeusia (40%), anemia (39%), AST/ALT elevation (38%), constipation (37%), vomiting (37%), diarrhea (32%), thrombocytopenia (29%), nasopharyngitis/upper respiratory tract infection (29%), stomatitis (28%), decreased appetite (23%), and neutropenia (20%).

Most common laboratory abnormalities in ARIEL3 ( $\geq$  25%; Grade 1-4) were increase in creatinine (98%), decrease in hemoglobin (88%), increase in cholesterol (84%), increase in alanine aminotransferase (ALT) (73%), increase in aspartate aminotransferase (AST) (61%), decrease in platelets (44%), decrease in leukocytes (44%), decrease in neutrophils (38%), increase in alkaline phosphatase (37%), and decrease in lymphocytes (29%).

## Select Important Safety Information (cont'd)

Most common adverse reactions in Study 10 and ARIEL2 ( $\geq 20\%$ ; Grade 1-4) were nausea (77%), asthenia/fatigue (77%), vomiting (46%), anemia (44%), constipation (40%), dysgeusia (39%), decreased appetite (39%), diarrhea (34%), abdominal pain (32%), dyspnea (21%), and thrombocytopenia (21%).

Most common laboratory abnormalities in Study 10 and ARIEL2 ( $\geq 35\%$ ; Grade 1-4) were increase in creatinine (92%), increase in alanine aminotransferase (ALT) (74%), increase in aspartate aminotransferase (AST) (73%), decrease in hemoglobin (67%), decrease in lymphocytes (45%), increase in cholesterol (40%), decrease in platelets (39%), and decrease in absolute neutrophil count (35%).

Co-administration of rucaparib can increase the systemic exposure of CYP1A2, CYP3A, CYP2C9, or CYP2C19 substrates, 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 frequency of international normalized ratio (INR) monitoring.

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 after the last dose.

You may report side effects to the FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch). You may also report side effects to Clovis Oncology, Inc. at 1-844-258-7662.

**Please see accompanying Prescribing Information for additional Important Safety Information.**

## 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 ( $\geq 20\%$ ) 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 ( $\geq 25\%$ ) 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](http://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

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## 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 ( $\leq$  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<sub>0-24h</sub> in patients receiving the recommended human dose of 600 mg twice daily. Advise 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**

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

<sup>a</sup> National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE version 4.03)

<sup>b</sup> 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  $\geq 25\%$  of Patients**

Laboratory Parameter <sup>a</sup>	Rubraca N=372		Placebo N=189	
	Grade 1-4 %	Grade 3-4 %	Grade 1-4 %	Grade 3-4 %
<b>Chemistry</b>				
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
<b>Hematology</b>				
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

<sup>a</sup> 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  $\geq 20\%$  of Patients with Ovarian Cancer After  $\geq 2$  Chemotherapies Treated with Rubraca in Study 10 and ARIEL2**

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

<sup>a</sup> 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 erythrodysesthesia syndrome (2%), and febrile neutropenia (1%).

**Table 5. Laboratory Abnormalities Reported in  $\geq 35\%$  of Patients with Ovarian Cancer After  $\geq 2$  Chemotherapies Treated with Rubraca in Study 10 and ARIEL2**

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

<sup>a</sup> At least one worsening shift in CTCAE grade and by maximum shift from baseline.

<sup>b</sup> 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<sub>0-24h</sub> 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<sub>0-24h</sub>).

### 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)*].

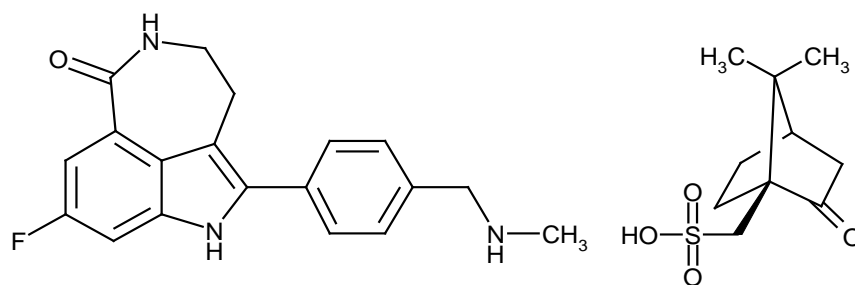
## **10 OVERDOSAGE**

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 95<sup>th</sup> percentile C<sub>max</sub> (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<sub>max</sub> was 1940 ng/mL (54% coefficient of variation [CV]) and AUC<sub>0-12h</sub> 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  $\leq 1.13$ -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 ( $AUC_{0-24h}$ ), 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  $\leq$  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 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 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 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)**

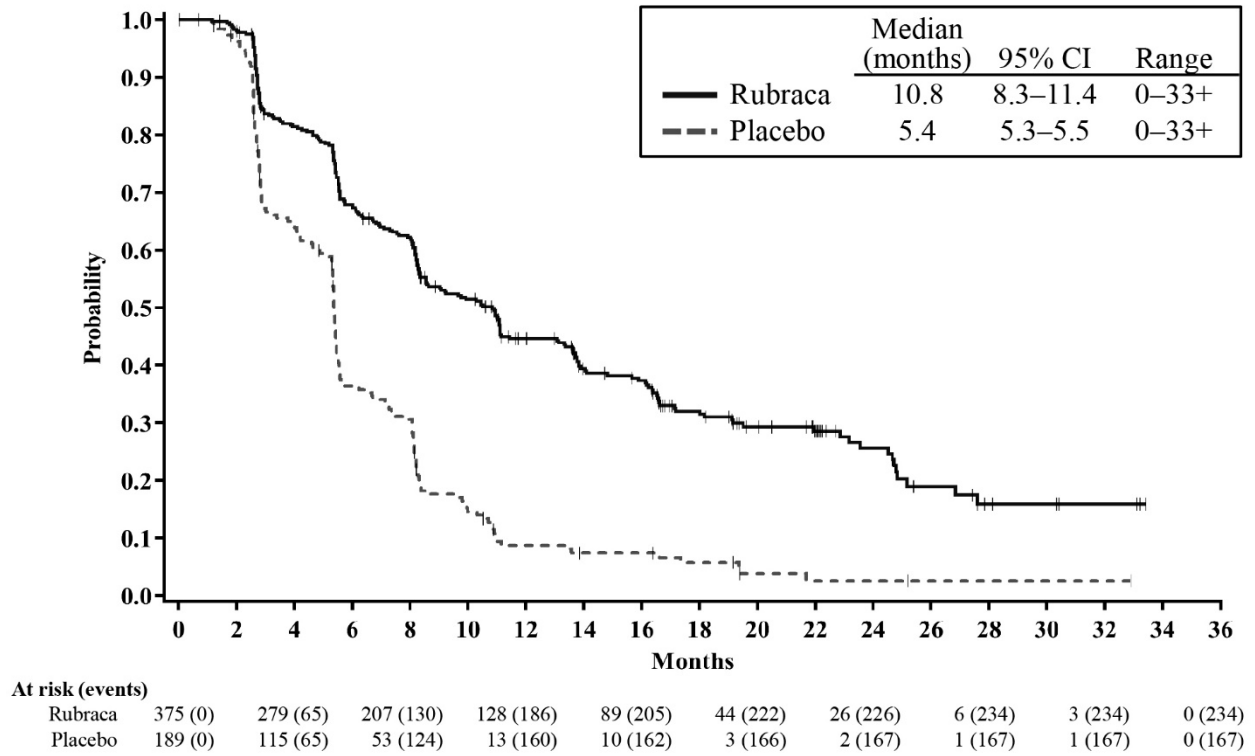
	<b>Rubraca</b>	<b>Placebo</b>
<b>All Patients<sup>a</sup></b>		
Patients, N	375	189
PFS events, n (%)	234 (62%)	167 (88%)
PFS, median in months	10.8	5.4
HR (95% CI)	0.36 (0.30, 0.45)	
p-value	< 0.0001	
<b>HRD Group<sup>b</sup></b>		
Patients, N	236	118
PFS events, n (%)	134 (57%)	101 (86%)
PFS, median in months	13.6	5.4
HR (95% CI)	0.32 (0.24, 0.42)	
p-value	< 0.0001	
<b>tBRCA Group<sup>c</sup></b>		
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.

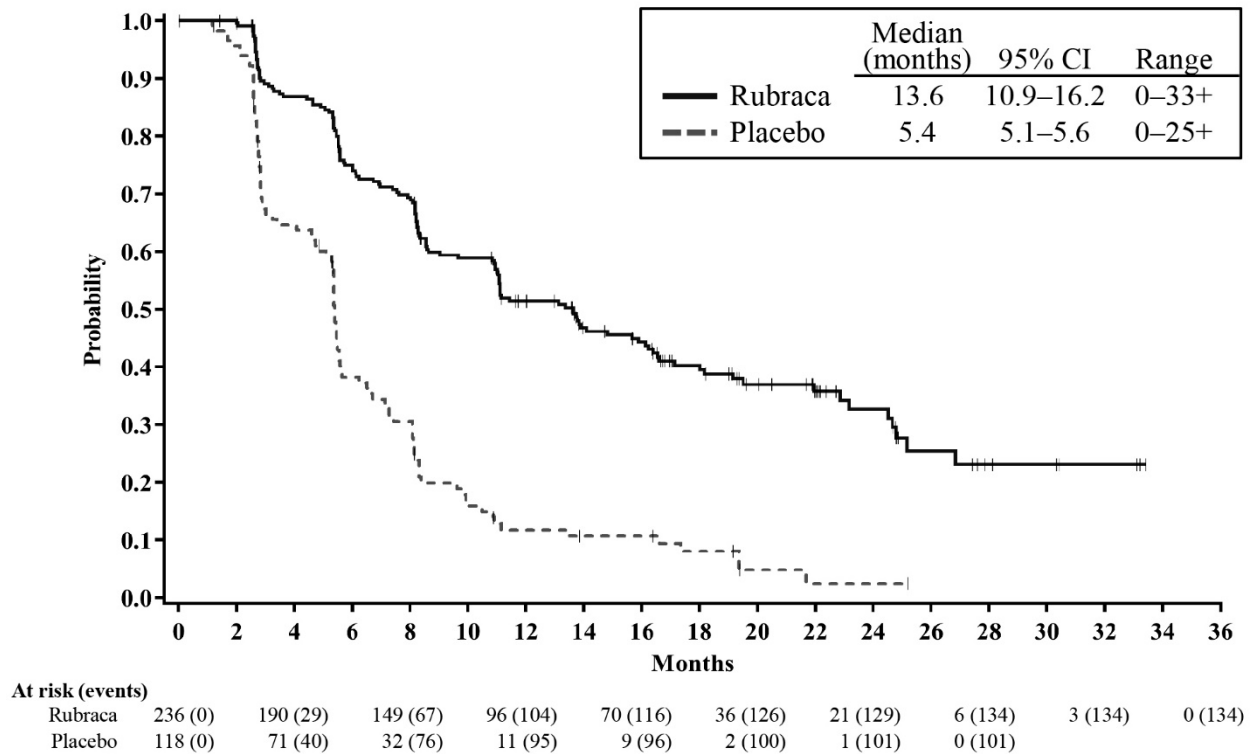
b. HRD includes all patients with a deleterious germline or somatic BRCA mutation or high genomic loss of heterozygosity, as determined by the CTA.

c. tBRCA includes all patients with a deleterious germline or somatic BRCA mutation, as determined by the CTA.

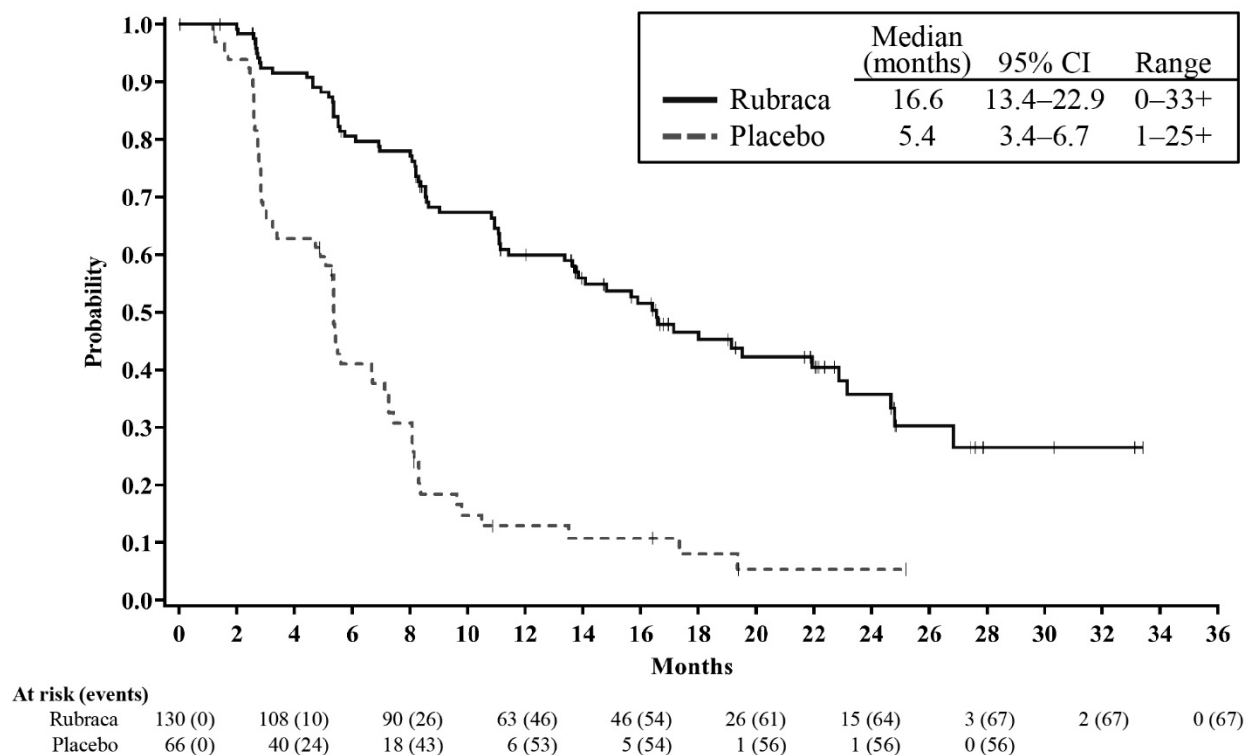
**Figure 1. Kaplan-Meier Curves of Progression-Free Survival in ARIEL3 as Assessed by Investigator: All Patients**



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



**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™ CD<sub>XBRCA</sub> 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

Rubraca is a registered trademark of Clovis Oncology, Inc.

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

Distributed by: Clovis Oncology, Inc. Boulder, Colorado 80301  
 For more information, go to [www.Rubraca.com](http://www.Rubraca.com) or call 1-844-258-7662.

This Patient Information has been approved by the U.S. Food and Drug Administration.

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