# Rubraca® (rucaparib) tablets access overview

## Simple steps to getting Rubraca

Your patients can receive Rubraca® (rucaparib) tablets through either your in-office dispensing (IOD) pharmacy or one of our network specialty pharmacies. Rubraca Connections can help determine eligibility for financial support and coordinate the process, and answer any questions you may have.

| | IOD PHARMACY | SPECIALTY PHARMACY |
|---|---|---|
| PRESCRIPTION  | Submit a Rubraca® (rucaparib) tablets prescription to your practice's IOD pharmacy via fax or online at RubracaConnections.com/iAssist | Complete a Rubraca prescription or the Rubraca Prescription Form and send to specialty pharmacy via fax or online at RubracaConnections.com/iAssist |
| ACCESS  | IOD pharmacies can order Rubraca from a wholesaler or specialty distributor (listed on RubracaConnections.com)<br><br>IOD pharmacy conducts benefits investigation<br>• If insurer requires use of a specialty pharmacy, please contact one from our network<br>• If specialty pharmacy is not required, IOD pharmacy coordinates prior authorization with insurance company | **Avella**<br>Phone: 877-546-5779 \| **Fax: 877-546-5780**<br>**Biologics**<br>Phone: 800-850-4306 \| **Fax: 800-823-4506**<br>**CVS Specialty**<br>Phone: 800-259-1783 \| **Fax: 855-296-0210**<br>**US Bioservices**<br>Phone: 877-757-0667 \| **Fax: 888-899-0067**<br><br>Specialty pharmacy conducts benefits investigation and coordinates prior authorization with insurance company |
| RUBRACA CONNECTIONS  | Rubraca Connections can help determine eligibility for financial support that may be available as well as facilitate or assist with enrollment. Rubraca Connections may also assist with reimbursement support, including benefits investigations, prior authorizations, and appeals | |

**Rubraca Connections financial support programs include:**

- **Rubraca $0 Co-Pay Program** for commercially insured patients
- **Rubraca Connections QuickStart Program** for commercial or government insured patients experiencing coverage delays*
- **Rubraca Connections Patient Assistance Program** for patients who are uninsured or rendered uninsured*

To get started, you can fax the Rubraca Prescription Form to 1-844-779-7717, submit online at RubracaConnections.com/iAssist, or call Rubraca Connections at 1-844-779-7707

*Patients must meet diagnosis and coverage criteria to be eligible. Visit RubracaConnections.com for complete Terms and Conditions and eligibility criteria.

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# Rubraca Connections is here to help your patients afford Rubraca

A Rubraca Connections Access Specialist can help eligible patients receive financial support. Assistance is available across all coverage types.

| Insurance type | Program |
|---|---|
| **Private/commercial insurance** | **Rubraca $0 Co-Pay Program***<br>• Patients with private/commercial insurance may have $0 out-of-pocket drug costs regardless of income<br>• Support of up to $30,000 per calendar year |
| **Government insurance (Medicare, Medicaid, and VA/DoD)** | **Independent co-pay support programs†‡**<br>• May provide assistance for some patients who do not qualify for the Rubraca $0 Co-Pay Program |
| **Uninsured or rendered uninsured** | **Rubraca Connections Patient Assistance Program†‡**<br>• Some patients may be eligible to receive Rubraca® (rucaparib) tablets at no cost<br>• Eligibility requirements include income level, diagnosis, US residency, type of insurance, and insurance status |

## Rubraca Connections QuickStart Program

The Rubraca Connections QuickStart Program may provide support to patients experiencing insurance delays of 5 business days or more. Eligible patients receive 15-day supplies of Rubraca for up to 60 days (2 months) during insurance coverage investigations.‡§

**For more information on financial support, please call 1-844-779-7707, Monday through Friday 8 AM to 8 PM ET. To complete the Rubraca Prescription Form, visit RubracaConnections.com.**

*The Rubraca $0 Co-Pay Program does not cover costs for any other medication, procedure, office visit, or diagnostic test. Commercially insured patients are eligible to participate in the Rubraca $0 Co-Pay Program for as long as they are treated with Rubraca. The Rubraca $0 Co-Pay Program is available for patients residing in the US, Puerto Rico, or US territories. See complete Terms and Conditions for eligibility criteria.

† Foundations are third-party independent 501(c)(3) organizations.

‡ Patients must meet diagnosis and coverage criteria to be eligible.

§ Product provided through this program may not be used for resale, dispensed to other patients, or billed to any insurance carrier.

CLOVIS ONCOLOGY



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## 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**

### INDICATIONS AND USAGE

RUBRACA is a poly (ADP-ribose) polymerase (PARP) inhibitor indicated as monotherapy for the treatment of patients with deleterious *BRCA* mutation (germline and/or somatic) associated advanced ovarian cancer who have been treated with two or more chemotherapies. Select patients for therapy based on an FDA-approved companion diagnostic for RUBRACA. (1, 2.1)

This indication is approved under accelerated approval based on objective response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. (1, 14)

### DOSAGE AND ADMINISTRATION

- Recommended dose is 600 mg orally twice daily with or without food. (2.2)
- Continue treatment until disease progression or unacceptable toxicity. (2.2)
- For adverse reactions, consider interruption of treatment or dose reduction. (2.3)

### 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, including one fatal event of AML. 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, abdominal pain, dysgeusia, constipation, decreased appetite, diarrhea, thrombocytopenia, and dyspnea. (6.1)
- Most common laboratory abnormalities (≥ 35%) were increase in creatinine, increase in ALT, increase in AST, decrease in hemoglobin, decrease in lymphocytes, increase in cholesterol, decrease in platelets, and decrease in absolute neutrophil count. (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.**

### USE IN SPECIFIC POPULATIONS

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

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

**Revised: 2/2017**

## FULL PRESCRIBING INFORMATION: CONTENTS*



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

## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

Rubraca™ is indicated as monotherapy for the treatment of patients with deleterious *BRCA* mutation (germline and/or somatic) associated advanced ovarian 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)]*.

This indication is approved under accelerated approval based on objective response rate and duration of response *[see Clinical Studies (14)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

### 2 DOSAGE AND ADMINISTRATION

#### 2.1 Patient Selection

Select patients for the treatment of advanced ovarian cancer with Rubraca based on the presence of a deleterious *BRCA* mutation (germline and/or somatic)*[see Indications and Usage (1) and Clinical Studies (14)]*. 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.

#### 2.2 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.

#### 2.3 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) |

### 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) was reported in 2 of 377 (0.5%) patients with ovarian cancer treated with Rubraca. The duration of Rubraca treatment prior to the diagnosis of MDS/AML was 57 days and 539 days. Both patients received prior treatment with platinum and other DNA damaging agents.

In addition, AML was reported in 2 (< 1%) patients with ovarian cancer enrolled in a blinded, randomized trial evaluating Rubraca versus placebo. One case of AML was fatal. The duration of treatment prior to the diagnosis of AML was 107 days and 427 days. Both patients had received prior treatment with platinum and other DNA damaging agents.

Monitor complete blood count testing at baseline and monthly thereafter. Do not start Rubraca until patients have recovered from hematological toxicity caused by previous chemotherapy (≤ Grade 1). For prolonged hematological toxicities, interrupt Rubraca and monitor blood counts weekly until recovery. If the levels have not recovered to Grade 1 or less after 4 weeks, 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 organogenesis resulted in embryo-fetal death at maternal exposure that were 0.04 times the $AUC_{0\text{-}24h}$ in patients receiving the recommended 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.

Rubraca 600 mg twice daily as monotherapy, has been studied in 377 patients with ovarian cancer treated in two open-label, single arm trials. In these patients, the median age was 62 years (range 31 to 86), 100% had an Eastern Cooperative Oncology Group (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).

Adverse reactions led to dose reduction or interruption in 62% of patients, most frequently from anemia (27%), and fatigue/asthenia (22%). Adverse reactions led to dose discontinuation in 10% of patients, most frequently from fatigue/asthenia (2%). The median duration of treatment was 5.5 months (range 0.1 to 28.0).

Table 2 and Table 3 summarize the common adverse reactions and abnormal laboratory findings, respectively, observed in patients treated with Rubraca.

**Table 2. Adverse Reactions Reported in ≥ 20% of Patients with Ovarian Cancer Treated with Rubraca 600 mg Twice Daily**

| | All Ovarian Cancer Patients (N = 377) % | |
|---|---|---|
| **Adverse Reaction** | **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 3. Laboratory Abnormalities Reported in ≥ 35% of Patients with Ovarian Cancer Treated with Rubraca 600 mg Twice Daily**

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

[a] At least one worsening shift in CTCAE grade and by maximum shift from baseline.

[b] Increase in ALT/AST led to treatment discontinuation in 0.3% of patients (1/377).

### 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 exposure 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 infant. Because of the potential for serious adverse reactions in breast-fed infants from Rubraca, advise lactating women not to breastfeed during treatment with Rubraca and for 2 weeks after the final 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 final dose of Rubraca.

#### 8.4 Pediatric Use

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

#### 8.5 Geriatric Use

One hundred and sixty (42%) of the 377 ovarian cancer patients in clinical trials of Rubraca were 65 years of age or older. No overall differences in safety were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out. The effectiveness of Rubraca in patients with *BRCA*-mutant ovarian cancer who were 65 years of age or older could not be assessed due to the small number of patients (N=38).

#### 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 of 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 (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)]*.

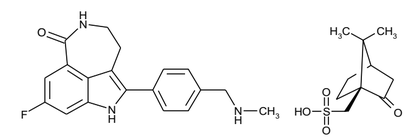
### 10 OVERDOSAGE

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 $C_{19}H_{18}FN_3O{\bullet}C_{10}H_{16}O_4S$ 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 cell death. Increased rucaparib-induced cytotoxicity 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 dosage) to 840 mg twice daily (1.4 times the approved recommended dosage). The mean QTcF increase from baseline (90% confidence interval [CI]) in population pharmacokinetics estimated 95$^{th}$ 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

All pharmacokinetics of rucaparib were 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 dosage. Accumulation was 3.5 to 6.2 fold. Median terminal half-life ($T_{1/2}$) was 17 hours following a single intravenous dose of 12 to 40 mg rucaparib.

Absorption

The median $T_{max}$ was 1.9 hours at the approved recommended dosage. 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 $AUC_{0\text{-}24h}$ 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 continuous 600 mg rucaparib orally 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 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 significant effect on rucaparib exposure.

*Renal Impairment*

In patients who received Rubraca 600 mg twice daily, those with mild renal impairment (N=148; 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

*Effects of Other Drugs on Rucaparib*

*In vitro*, rucaparib had a low metabolic turnover rate in human liver microsomes, and was metabolized primarily by CYP2D6 and to a lesser extent by CYP1A2 and CYP3A4. *In vitro*, rucaparib was shown to be a substrate of P-gp and BCRP, but not a substrate of renal uptake transporters OAT1, OAT3, and OCT2, or hepatic transporters OATP1B1 and OATP1B3.

Concomitant treatment with proton pump inhibitors has no clinically meaningful change in steady-state exposures.

*Effect of Rucaparib on Other Drugs*

Effect of rucaparib on other drugs has not been studied in humans. Rucaparib reversibly inhibited CYP1A2, CYP2C19, CYP2C9, and CYP3A, and to a lesser extent CYP2C8, CYP2D6, and UGT1A1. Rucaparib induced CYP1A2, and down regulated CYP2B6 and CYP3A4 in human hepatocytes at clinically relevant exposures. Rucaparib was a potent inhibitor of MATE1 and MATE2-K, and a moderate inhibitor of OCT1. Weak inhibition was observed at ultra-therapeutic concentration (300 µM) of rucaparib for MRP4, OATP1B1, OATP1B3, OAT1, and OAT3. No inhibition was observed for MRP2, MRP3, or BSEP. Rucaparib was an inhibitor of BCRP and P-gp efflux transporters with $IC_{50}$ of 55 µM and 283 µM, respectively.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with rucaparib.

Rucaparib was mutagenic in a bacterial reverse mutation (Ames) test, and 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.

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

The efficacy of Rubraca was investigated in 106 patients in two multicenter, single-arm, open-label clinical trials, Study 1 and Study 2, 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 independent radiology review (IRR) according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.

The median age of the patients was 59 years (range 33 to 84), the majority were Caucasian (78%), and 100% had an Eastern Cooperative Oncology Group (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 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 4.

**Table 4. Overall Response and Duration of Response in Patients with *BRCA*-mutant Ovarian Cancer Who Received 2 or More Chemotherapies in Study 1 and Study 2**

| | 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:
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**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 ovarian 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 to treat people with advanced ovarian cancer who:

- have certain "*BRCA*" gene mutations, either inherited (germline) or acquired (somatic), and
- have received previous treatment with 2 or more prior 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.

**What should I tell my healthcare provider before taking Rubraca?**

**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 your breast milk. Do not breastfeed during treatment and for 2 weeks after the last dose of Rubraca.

**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
- fatigue
- vomiting
- stomach-area pain
- changes in how food tastes
- constipation
- decreased appetite
- diarrhea
- shortness of breath
- decrease in hemoglobin (anemia)
- low blood cell counts
- changes in liver or kidney function blood tests
- 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 at 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, 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.

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