ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Rubraca 200 mg film-coated tablets
Rubraca 250 mg film-coated tablets
Rubraca 300 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Rubraca 200 mg film-coated tablets

Each tablet contains rucaparib camsylate corresponding to 200 mg rucaparib.

Rubraca 250 mg film-coated tablets

Each tablet contains rucaparib camsylate corresponding to 250 mg rucaparib.

Rubraca 300 mg film-coated tablets

Each tablet contains rucaparib camsylate corresponding to 300 mg rucaparib.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Rubraca 200 mg film-coated tablet

Blue, 11 mm, round film-coated tablet, debossed with “C2”.

Rubraca 250 mg film-coated tablet

White, 11 × 15 mm, diamond-shaped film-coated tablet, debossed with “C25”.

Rubraca 300 mg film-coated tablet

Yellow, 8 × 16 mm, oval film-coated tablet, debossed with “C3”.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rubraca is indicated as monotherapy for the maintenance treatment of adult patients with advanced (FIGO Stages III and IV) high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy.

Rubraca is indicated as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy.

4.2 Posology and method of administration

Treatment with Rubraca should be initiated and supervised by a physician experienced in the use of anticancer medicinal products.

Posology

The recommended dose of Rubraca is 600 mg taken twice daily, equivalent to a total daily dose of 1 200 mg.

Patients should start the maintenance treatment with Rubraca no later than 8 weeks after completion of their final dose of the platinum containing regimen.

Duration of treatment
First-line maintenance treatment of advanced ovarian cancer:
Patients can continue treatment until disease progression, unacceptable toxicity or completion of 2 years treatment.

Maintenance treatment of platinum-sensitive relapsed ovarian cancer:
Patients can continue treatment until disease progression or unacceptable toxicity.

If a patient vomits after taking Rubraca, the patient should not retake the dose and should take the next scheduled dose.

Missed doses
If a dose is missed, the patient should resume taking Rubraca with the next scheduled dose.

Dose adjustments for adverse reactions

Adverse reactions may be managed through dose interruptions and/or dose reductions for moderate to severe reactions (i.e. CTCAE Grade 3 or 4) such as neutropenia, anaemia and thrombocytopenia.

Liver transaminase elevations (aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT)) occur early in treatment and are generally transient. Grade 1 to 3 elevations in AST/ALT can be managed without change to the rucaparib dose, or with treatment modification (interruption and/or dose reduction). Grade 4 reactions require treatment modification (see Table 2).

Other moderate to severe non-haematological adverse reactions such as nausea and vomiting, can be managed through dose interruption and/or reductions, if not adequately controlled by appropriate symptomatic management.

Table 1. Recommended dose adjustments

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

Table 2. Management of Treatment-emergent AST/ ALT Elevations

Grade of AST/ALT Elevation	Management
Grade 3 without other signs of liver dysfunction	Monitor LFTs weekly until resolution to Grade ≤ 2 Continue rucaparib provided bilirubin is < ULN and alkaline phosphatase is < 3 × ULN Interrupt treatment if AST/ALT levels do not decline within 2 weeks until Grade ≤ 2, then resume rucaparib at the same or at a reduced dose
Grade 4	Interrupt rucaparib until values return to Grade ≤ 2; then resume rucaparib with a dose reduction and monitor LFTs weekly for 3 weeks

Special populations

Elderly
No adjustment is recommended to the starting dose for elderly patients (≥ 65 years of age) (see sections 4.8 and 5.2). Greater sensitivity of some elderly patients (≥ 65 years of age) to adverse events cannot be ruled out. There are limited clinical data in patients aged 75 or over.

Hepatic impairment
No starting dose adjustment is required in patients with mild or moderate hepatic impairment (see section 5.2). Patients with moderate hepatic impairment should be carefully monitored for hepatic function and adverse reactions. There are no clinical data in patients with severe hepatic impairment (i.e., total bilirubin > 3 times ULN), therefore rucaparib is not recommended for use in patients with severe hepatic impairment.

Renal impairment
No starting dose adjustment is required in patients with mild or moderate renal impairment (see section 5.2). There are no clinical data in patients with severe renal impairment (CLcr less than 30 mL/min), therefore rucaparib is not recommended for use in patients with severe renal impairment. Rucaparib may only be used in patients with severe renal impairment if the potential benefit outweighs the risk. Patients with moderate or severe renal impairment should be carefully monitored for renal function and adverse reactions.

Paediatric population
The safety and efficacy of Rubraca in children or adolescents aged less than 18 years have not been established. No data are available.

Method of administration

Rubraca is for oral use and can be taken with or without food. The doses should be taken approximately 12 hours apart. See section 5.2.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Breast-feeding (see section 4.6).

4.4 Special warnings and precautions for use

Haematological toxicity

During treatment with rucaparib, events of myelosuppression (anaemia, neutropenia, thrombocytopenia) may be observed and are typically first observed after 8 to 10 weeks of treatment with rucaparib. These reactions are manageable with routine medical treatment and/or dose adjustment

for more severe cases. Complete blood count testing prior to starting treatment with Rubraca, and monthly thereafter, is advised. Patients should not start Rubraca treatment until they have recovered from haematological toxicities caused by previous chemotherapy (≤ CTCAE Grade 1).

Supportive care and institutional guidelines should be implemented for the management of low blood counts for the treatment of anaemia and neutropenia. Rubraca should be interrupted or dose reduced according to Table 1 (see section 4.2) and blood counts monitored weekly until recovery. If the levels have not recovered to CTCAE Grade 1 or better after 4 weeks, the patient should be referred to a haematologist for further investigations.

Myelodysplastic syndrome/acute myeloid leukaemia

Myelodysplastic syndrome/acute myeloid leukaemia (MDS/AML), including cases with fatal outcome, have been reported in patients who received rucaparib. The duration of therapy with rucaparib in patients who developed MDS/AML varied from < 2 months to approximately 6 years.

If MDS/AML is suspected, the patient should be referred to a haematologist for further investigations, including bone marrow analysis and blood sampling for cytogenetics. If, following investigation for prolonged haematological toxicity, MDS/AML is confirmed, Rubraca should be discontinued.

Photosensitivity

Photosensitivity has been observed in patients treated with rucaparib. Patients should avoid spending time in direct sunlight because they may burn more easily during rucaparib treatment; when outdoors, patients should wear a hat and protective clothing, and use sunscreen and lip balm with sun protection factor (SPF) of 50 or greater.

Gastrointestinal toxicities

Gastrointestinal toxicities (nausea and vomiting) are frequently reported with rucaparib, are generally low grade (CTCAE Grade 1 or 2) and may be managed with dose reduction (refer to Table 1) or interruption. Antiemetics, such as 5-HT3 antagonists, dexamethasone, aprepitant and fosaprepitant, can be used as treatment for nausea/vomiting and may also be considered for prophylactic (i.e., preventative) use prior to starting Rubraca. It is important to proactively manage these events to avoid prolonged or more severe events of nausea/vomiting which have the potential to lead to complications such as dehydration or hospitalisation.

Intestinal obstruction

Cases of intestinal obstruction have been observed in ovarian cancer patients treated with rucaparib in clinical trials; 3.5% of patients treated with rucaparib experienced a serious event of intestinal obstruction, with a fatal outcome in 1 rucaparib treated patient (less than 0.1%). The underlying disease may play a role in the development of intestinal obstruction in patients with ovarian cancer. In the event of suspected intestinal obstruction, a prompt diagnostic evaluation should be conducted and the patient should be treated appropriately.

Embryofoetal toxicity

Rubraca can cause foetal 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-foetal toxicity at exposures below those in patients receiving the recommended human dose of 600 mg twice daily (see section 5.3).

Pregnancy/contraception

Pregnant women should be informed of the potential risk to a foetus. Women of reproductive potential should be advised to use effective contraception during treatment and for 6 months following the last dose of Rubraca (see section 4.6). A pregnancy test before initiating treatment is recommended in women of reproductive potential.

Excipients

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of other medicinal products on rucaparib

Enzymes responsible for rucaparib metabolism have not been identified. Based on *in vitro* data, CYP2D6, and to a lesser extent CYP1A2 and CYP3A4, were able to metabolize rucaparib. Although *in vitro* rucaparib metabolism mediated by CYP3A4 was slow, a significant contribution of CYP3A4 *in vivo* cannot be excluded. Caution should be used for concomitant use of strong CYP3A4 inhibitors or inducers.

In vitro, rucaparib was shown to be a substrate of P-gp and BCRP. Effect of P-gp and BCRP inhibitors on rucaparib PK cannot be ruled out. Caution is recommended when rucaparib is co-administered with medicinal products that are strong inhibitors of P-gp.

Effects of rucaparib on other medicinal products

In medicinal product interaction studies in cancer patients, the effects of steady-state rucaparib at 600 mg twice daily on CYP1A2, CYP2C9, CYP2C19, CYP3A, BCRP and P-gp were evaluated with single oral doses of sensitive probes (caffeine, S-warfarin, omeprazole, midazolam, rosuvastatin, and digoxin, respectively). The effect of rucaparib on the pharmacokinetics of the combined oral contraceptive (ethinylestradiol and levonorgestrel) was also evaluated. Data suggest that rucaparib is a moderate inhibitor of CYP1A2, and a mild inhibitor of CYP2C9, CYP2C19, and CYP3A. Rucaparib also marginally inhibits P-gp and weakly inhibits BCRP in the gut.

CYP1A2 substrates
Rucaparib showed no effect on C_{max} of caffeine while moderately increasing AUC_{inf} of caffeine by 2.55 fold (90% CI: 2.12, 3.08). When co-administering medicinal products metabolized by CYP1A2, particularly medicines which have a narrow therapeutic index (e.g., tizanidine, theophylline), dose adjustments may be considered based on appropriate clinical monitoring.

CYP2C9 substrates
Rucaparib increased S-warfarin C_{max} by 1.05 fold (90% CI: 0.99 to 1.12) and $AUC_{0\text{-}96\ h}$ by 1.49 fold (90% CI: 1.40 to 1.58), respectively. When co-administering medicinal products that are CYP2C9 substrates with a narrow therapeutic index (e.g., warfarin, phenytoin), dose adjustments may be considered, if clinically indicated. Caution should be exercised and additional International Normalised Ratio (INR) monitoring with co-administration of warfarin and therapeutic drug level monitoring of phenytoin should be considered, if used concomitantly with rucaparib.

CYP2C19 substrates
Rucaparib increased omeprazole C_{max} by 1.09 fold (90% CI: 0.93 to 1.27) and AUC_{inf} by 1.55 fold (90% CI: 1.32 to 1.83). The risk for a clinically relevant effect of concomitant administration of proton pump inhibitors (PPIs) is likely small (see section 5.2). No dose adjustment is considered necessary for co-administered medicinal products that are CYP2C19 substrates.

CYP3A substrates
Rucaparib increased midazolam C_{max} by 1.13 fold (90% CI: 0.95 to 1.36) and AUC_{inf} by 1.38 fold (90% CI: 1.13 to 1.69). Caution is advised when co-administering medicinal products that are CYP3A substrates with a narrow therapeutic index (e.g., alfentanil, astemizole, cisapride, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, terfenadine). Dose adjustments may be considered, if clinically indicated based on observed adverse reactions.

Oral contraceptives
Rucaparib increased ethinylestradiol C_{max} by 1.09 fold (90% CI: 0.94 to 1.27) and AUC_{last} by 1.43 fold (90% CI: 1.15 to 1.77). Rucaparib increased levonorgestrel C_{max} by 1.19 fold (90% CI: 1.00 to 1.42) and AUC_{last} by 1.56 fold (90% CI: 1.33 to 1.83). No dose adjustment is recommended for co-administered oral contraceptives.

BCRP substrates
Rucaparib increased rosuvastatin C_{max} by 1.29 fold (90% CI: 1.07 to 1.55) and AUC_{inf} by 1.35 fold (90% CI: 1.17 to 1.57). No dose adjustment is recommended for co-administered medicinal products that are BCRP substrates.

P-gp substrates
Rucaparib showed no effect on C_{max} of digoxin while marginally increasing $AUC_{0\text{-}72\ h}$ by 1.20 fold (90% CI: 1.12 to 1.29). No dose adjustment is recommended for co-administered medicinal products that are P-gp substrates.

Interaction of rucaparib with other enzymes and transporter was evaluated *in vitro*. Rucaparib is a weak inhibitor of CYP2C8, CYP2D6, and UGT1A1. Rucaparib down regulated CYP2B6 in human hepatocytes at clinically relevant exposures. Rucaparib is a potent inhibitor of MATE1 and MATE2-K, a moderate inhibitor of OCT1, and a weak inhibitor of OCT2. As inhibition of these transporters could decrease metformin renal elimination and decrease liver uptake of metformin, caution is advised when metformin is co-administered with rucaparib. The clinical relevance of UGT1A1 inhibition by rucaparib is not clear. Caution should be used when rucaparib is co-administered with UGT1A1 substrates (i.e. irinotecan) to patients with UGT1A1*28 (poor metabolizer) due to a possible increase in the exposure of SN-38 (the active metabolite of irinotecan) and associated toxicities.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/contraception in females

Women of childbearing potential should be advised to avoid becoming pregnant while receiving rucaparib. Patients should be advised to use effective contraception during treatment and for 6 months following the last dose of rucaparib (see section 4.5).

Pregnancy

There are no or limited data from the use of rucaparib in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Based on its mechanism of action and preclinical data, rucaparib may cause foetal harm when administered to a pregnant woman. Rubraca should not be used during pregnancy unless the clinical condition of the woman requires treatment with rucaparib. A pregnancy test before initiating treatment is recommended in women of reproductive potential.

Breast-feeding

There are no animal studies on the excretion of rucaparib in breast milk. It is unknown whether rucaparib/or its metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded. Rubraca must not be used during breast-feeding.

Because of the potential for serious adverse reactions in breast-fed infants from rucaparib,

breast-feeding is contraindicated during treatment with Rubraca and for 2 weeks after the final dose (see section 4.3).

Fertility

There are no data on the effect of rucaparib on human fertility. Based on the animal studies, impact on fertility associated with the use of rucaparib cannot be ruled out (see section 5.3). Moreover, according to its mechanism of action, rucaparib may impact human fertility.

4.7 Effects on ability to drive and use machines

Rubraca has minor influence on the ability to drive and use machines. Caution when driving or using machines is advised for patients who report fatigue, nausea, or dizziness during treatment with Rubraca (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The overall safety profile of rucaparib is based on data from 1 594 patients in clinical trials in ovarian cancer treated with rucaparib monotherapy. Patients were exposed to rucaparib for a median of 7.4 months.
Adverse reactions occurring in ≥ 20% of patients receiving rucaparib were nausea, fatigue/asthenia, vomiting, anaemia, abdominal pain, dysgeusia, ALT elevations, AST elevations, decreased appetite, diarrhoea, neutropenia and thrombocytopenia. The majority of adverse reactions were mild to moderate (Grade 1 or 2).

The ≥ Grade 3 adverse reactions occurring in > 5% of patients were anaemia (25%), ALT elevations (10%), neutropenia (10%), fatigue/asthenia (9%), and thrombocytopenia (7%). The only serious adverse reaction occurring in > 2% of patients was anaemia (5%).

Adverse reactions that most commonly led to dose reduction or interruption were anaemia (23%), fatigue/asthenia (15%), nausea (14%), thrombocytopenia (14%), neutropenia (10%) and AST/ALT elevations (10%). Adverse reactions leading to permanent discontinuation occurred in 15% of patients; with the most frequently reported being thrombocytopenia, nausea, anaemia, and fatigue/asthenia.

Tabulated list of adverse reactions

The adverse reaction frequency is listed by MedDRA System Organ Class (SOC) at the preferred term level. Frequencies of occurrence of adverse reactions are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000), not known (cannot be estimated from the available data).

Table 3. Tabulated list of adverse reactions by MedDRA system organ class

	Adverse reactions	
MedDRA system organ class	**Frequency of all CTCAE grades**	**Frequency of CTCAE grade 3 and above**
Neoplasms benign, malignant and unspecified (including cysts and polyps)	**Common** Myelodysplastic syndrome / Acute myeloid leukaemia [a]	**Common** Myelodysplastic syndrome / Acute myeloid leukaemia [a]
Blood and lymphatic system disorders	**Very common** Anaemia [b], Thrombocytopenia [b], Neutropenia [b], Leukopenia [b] **Common** Lymphopenia [b], Febrile neutropenia	**Very common** Anaemia [b], Neutropenia [b] **Common** Thrombocytopenia [b], Febrile neutropenia, Leukopenia [b], Lymphopenia [b]

Immune system disorders	**Common** Hypersensitivity [c]	**Uncommon** Hypersensitivity [c]
Metabolism and nutrition disorders	**Very common** Decreased appetite, Increased blood creatinine [b], Hypercholesterolaemia [b], **Common** Dehydration	**Common** Decreased appetite, Dehydration, Hypercholesterolaemia [b] **Uncommon** Increased blood creatinine [b]
Nervous system disorders	**Very common** Dysgeusia, Dizziness	**Uncommon** Dysgeusia, Dizziness
Respiratory, thoracic and mediastinal disorders	**Very common** Dyspnoea	**Uncommon** Dyspnoea
Gastrointestinal disorders	**Very common** Nausea, Vomiting, Diarrhoea, Dyspepsia, Abdominal pain **Common** Intestinal obstruction [d], Stomatitis	**Common** Nausea, Vomiting, Diarrhoea, Abdominal pain, Intestinal obstruction [d] **Uncommon** Dyspepsia, Stomatitis
Hepatobiliary disorders	**Very common** Increased alanine aminotransferase, Increased aspartate aminotransferase **Common** Increased transaminases [b]	**Common** Increased alanine aminotransferase, Increased aspartate aminotransferase **Uncommon** Increased transaminases [b]
Skin and subcutaneous tissue disorders	**Very common** Photosensitivity reaction, Rash **Common** Rash maculo-papular, Palmar-plantar erythrodysaesthesia syndrome, Erythema	**Uncommon** Photosensitivity reaction, Rash, Rash maculo-papular, Palmar-plantar erythrodysaesthesia syndrome
General disorders and administration site conditions	**Very common** Fatigue [e], Pyrexia	**Common** Fatigue [e] **Uncommon** Pyrexia

a MDS/AML rate is based on overall total patient population of 3 025 who have received one dose of oral rucaparib.
b Includes laboratory findings
c Most commonly observed events include hypersensitivity, drug hypersensitivity and swelling/oedema of the face and eyes.
d Includes intestinal obstruction, large intestinal obstruction, and small intestinal obstruction
e Includes fatigue, asthenia and lethargy

Description of selected adverse reactions

Haematological toxicity
Haematological adverse reactions of all CTCAE Grades of anaemia, thrombocytopenia and neutropenia were reported in 46%, 26% and 21% of patients, respectively. Anaemia and thrombocytopenia led to discontinuation in 2% and 1% of patients, respectively. Adverse reactions CTCAE Grade 3 or higher occurred in 25% (anaemia), 10% (neutropenia) and 7% (thrombocytopenia) of patients. The time of onset for adverse reactions of myelosuppression Grade 3 or higher was generally later in treatment (after 2 or more months). For risk mitigation and management, see section 4.4.

Myelodysplastic syndrome/Acute myeloid leukaemia
MDS/AML are serious adverse reactions that occur uncommonly (0.5%) in patients on treatment and during the 28 day safety follow up, and commonly (1.1%) for all patients including during the long term safety follow up (rate is calculated based on overall safety population of 3 025 patients exposed

to at least one dose of oral rucaparib in all clinical studies). In the placebo-controlled Phase 3 studies, ARIEL3 and ATHENA-MONO, the incidence of MDS/AML during therapy in patients who received rucaparib was 1.6% and 0.5%, respectively. Although no cases were reported during therapy in patients who received placebo, six cases have been reported in placebo-treated patients during the long term safety follow up. All patients had potential contributing factors for the development of MDS/AML; in all cases, patients had received previous platinum-containing chemotherapy regimens and/or other DNA damaging agents. For risk mitigation and management, see section 4.4.

Gastrointestinal toxicities
Vomiting and nausea were reported in 37% and 68% of patients, respectively, and were generally low grade (CTCAE Grade 1 to 2). Abdominal pain (combined terms abdominal pain, abdominal pain lower, abdominal pain upper) was reported in 39% of rucaparib treated patients, but was also very common (34%) in placebo patients, most likely associated with underlying disease. For risk mitigation and management, see section 4.4.

Photosensitivity
Photosensitivity was reported in 10% of patients as low grade skin reactions (CTCAE Grade 1 or 2), and by 0.2% of patients as ≥ CTCAE Grade 3 reaction. For risk mitigation and management, see section 4.4.

Increases in serum aminotransferases (AST/ALT)
Events related to increases in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) were observed in 39% (all grades) and 10% (≥ CTCAE Grade 3) of patients. These events occurred within the first few weeks of treatment with rucaparib, were reversible, and were rarely associated with increases in bilirubin. Increased ALT was observed in 37% (all grades) and 10% (≥ CTCAE Grade 3) of patients; increased AST in 33% (all grades) and 3% (≥ CTCAE Grade 3) of patients and increased ALT and AST in 31% (all grades) and 3% (≥ CTCAE Grade 3) of patients. No events met Hy's Law criteria for drug-induced liver injury. AST/ALT elevations may need to be managed with treatment interruption and/or dose reduction as described in Table 2 (see section 4.2). Most patients could continue rucaparib with or without treatment modification without recurrence of Grade ≥ 3 LFT abnormalities.

Elevations in serum creatinine
Increases in serum creatinine, predominantly mild to moderate (CTCAE Grade 1 or 2), were observed in 17% of patients within the first few weeks of treatment with rucaparib; 0.6% of patients reported a CTCAE Grade 3 reaction. Elevations in creatinine with rucaparib treatment may be due to inhibition of the renal transporters MATE1 and MATE2-K (see section 4.5). These increases in serum creatinine were clinically asymptomatic.

Elderly
In patients ≥ 75 years old, frequencies of some adverse reactions increased: increased blood creatinine (33%), dizziness (19%), pruritus (16%), and memory impairment (4%) were higher than in patients < 75 years old (16%, 14%, 11% and 1%, respectively).

Patients with Renal Impairment
In patients with moderate renal impairment (CLcr of 30-59 mL/min), frequencies of some adverse reactions of Grade 3 or above severity increased: anaemia (34%), neutropenia (13%), thrombocytopenia (12%), fatigue/asthenia (12%) and combined AST/ALT increased (12%) were higher than in patients with normal renal function (CLcr > 90 mL/min) (23%, 8%, 5%, 7% and 7%, respectively).

Paediatric population

No studies have been conducted to investigate the pharmacokinetics of rucaparib in paediatric patients.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antineoplastic agents, ATC code: L01XK03

Mechanism of action and pharmacodynamics effects

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 involves inhibition of PARP enzymatic activity and the trapping of PARP-DNA complexes resulting in increased DNA damage, apoptosis, and cell death.

Rucaparib has been shown to have *in vitro* and *in vivo* anti-tumour activity in BRCA mutant cell lines through a mechanism known as synthetic lethality, whereby the loss of two DNA repair pathways is required for cell death. Increased rucaparib-induced cytotoxicity and anti-tumour activity was observed in tumour cell lines with deficiencies in BRCA1/2 and other DNA repair genes. Rucaparib has been shown to decrease tumour growth in mouse xenograft models of human cancer with or without deficiencies in BRCA.

Clinical efficacy

First-Line maintenance treatment of advanced ovarian cancer
The efficacy of rucaparib was evaluated in ATHENA, a Phase 3, double-blind, multicentre trial in which 538 patients with advanced ovarian (EOC), fallopian tube (FTC), or primary peritoneal cancer (PPC) who were in response to first-line platinum-based chemotherapy and surgery were enrolled. Response was defined as no evidence of disease progression radiologically or through rising CA-125 (per Gynecological Cancer Intergroup (GCIG) guidelines) at any time during first-line treatment; and either no evidence of measurable disease by RECIST v1.1, if complete resection after surgery, or a response (complete or partial) if measurable disease was present after surgery and prior to chemotherapy, or a GCIG CA-125 response if non-measurable disease was present in the same situation.

All patients had received between 4 to 8 cycles of platinum-doublet treatment (including ≥ 4 cycles of platinum/taxane combination). Bevacizumab treatment was allowed during first-line chemotherapy, but not during the maintenance rucaparib treatment. All patients were randomised within 8 weeks of the first day of the last cycle of chemotherapy.
Patients were randomised (4:1) to receive rucaparib tablets 600 mg orally twice daily (n=427) or placebo (n=111). Treatment was continued until disease progression or unacceptable toxicity or for up to 2 years. Randomisation was stratified by disease status post-chemotherapy (residual disease vs. no residual disease), timing of surgery (primary surgery vs. interval debulking), and biomarker status. Biomarker status was determined using the homologous recombination deficiency (HRD) test where biomarker-positive was a tumour with HRD defined by the presence of a deleterious tumour *BRCA*

(tBRCA) mutation or tBCRA wild type (tBRCAwt) / high genomic loss of heterozygosity (LOH^{high}), and biomarker-negative was a tumour without HRD, defined by tBRCAwt / low genomic LOH (LOH^{low}).

The major efficacy outcome was investigator-assessed progression-free survival (invPFS) evaluated according to Response Evaluation Criteria in Solid Tumours (RECIST), version 1.1. Key Secondary efficacy endpoints included overall survival (OS) and objective response rate (ORR) according to RECIST version 1.1. invPFS, OS and ORR testing were performed hierarchically: first in the HRD Group, then in the ITT population. Time from randomisation to second progression or death (PFS2), was an additional outcome measure.

The median age of patients treated with rucaparib was 61 years (range: 30 to 83) and 62 years (range: 31 to 80) among patients on placebo. The Eastern Cooperative Oncology Group **(**ECOG**)** performance status was 0 in 69% of patients receiving rucaparib and 68% of patients receiving placebo. Of the 538 patients randomised to rucaparib or placebo, 75% had FIGO Stage III disease and 25% had Stage IV disease, and 16% were in complete response to their most recent platinum-based regimen. Of the 538 patients randomised to rucaparib or placebo 78% had EOC, 13% had FTC and 9% had PPC, most patients (> 90%) had tumours with serous histology. In the ITT population, patients received a median of 6 cycles of platinum doublet chemotherapy and 17.8% of patients had received bevacizumab during first-line chemotherapy. Primary debulking surgery had been performed in 48.1% of patients, and 51.9% of patients had undergone neo-adjuvant chemotherapy followed by interval debulking surgery.

Overall, 43% had HRD (21% had a deleterious tBRCA mutation and 22% had $tBRCA^{wt}$ / LOH^{high}), 44% were HRD negative ($tBRCA^{wt}$ / LOH^{low}), and 12% had an unknown HRD status.

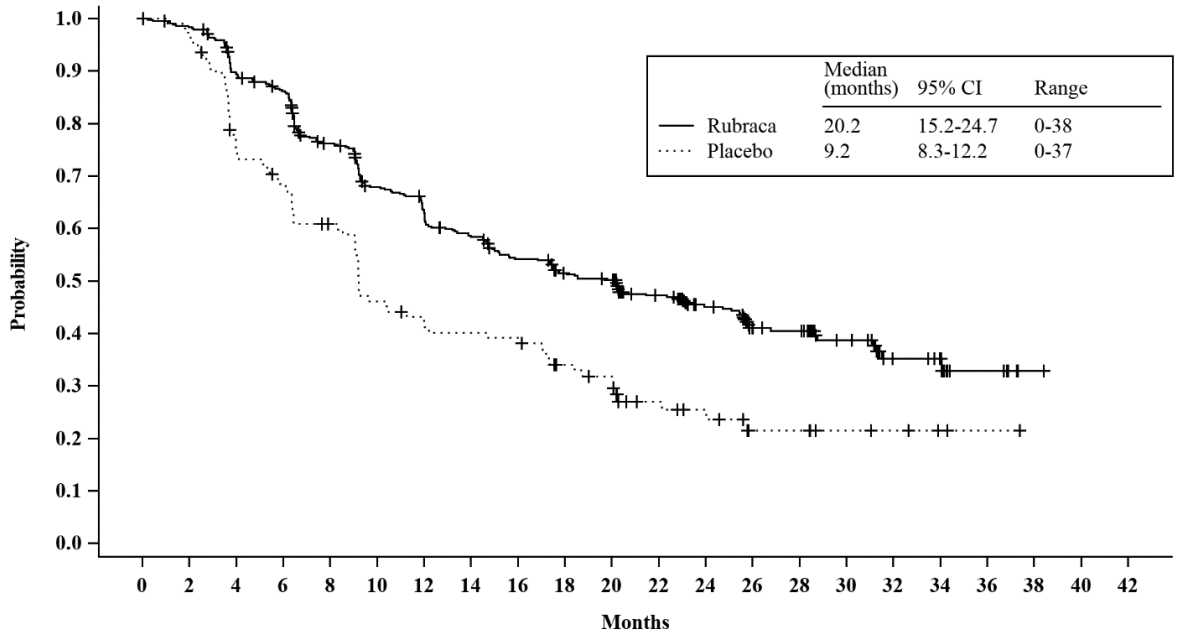
ATHENA demonstrated a statistically significant improvement in invPFS for patients randomised to rucaparib as compared with placebo in the HRD Group and the ITT Population. Results for invPFS with and without censoring for new anti-cancer treatment and missed visits were consistent. Efficacy results are presented in Table 4 and Figures 1 and Figure 2.

Table 4. Efficacy Results – ATHENA (Investigator Assessment)

	HRD Group[a]		ITT Population[b]	
	Rubraca (n = 185)	**Placebo (n = 49)**	**Rubraca (n = 427)**	**Placebo (n = 111)**
PFS[c] events, n (%)	80 (43.2)	31 (63.3)	230 (53.9)	78 (70.3)
PFS median in months (95% CI)	28.7 (23.0, NR)	11.3 (9.1,22.1)	20.2 (15.2,24.7)	9.2 (8.3,12.2)
Hazard ratio (95% CI)	0.47 (0.31, 0.72)		0.52 (0.40, 0.68)	
P- value[d]	0.0005		<0.0001	
OS[e] events, n (%)	46 (24.9)	12 (24.5)	144 (33.7)	42 (37.8)
OS median in months	NR	NR	NR	46.2
Hazard ratio (95% CI)	0.84 (0.44, 1.58)		0.83 (0.58, 1.17)	
P- value[d]	0.5811		0.2804	

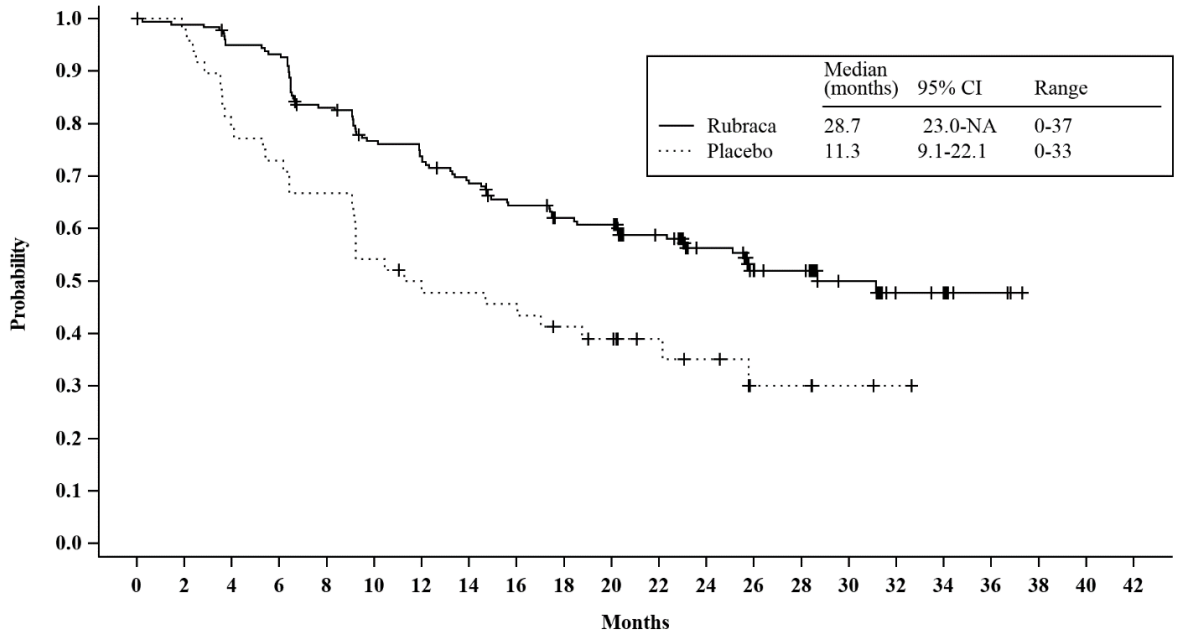
a Includes all patients with a deleterious tBRCA mutation (N=115) or tBRCAwt / LOHhigh (N=119).
b All randomised patients.
c The median follow up time was 26 months for both the rucaparib and placebo arms.
d P-value based on the stratified logrank test.
e At the time of the second interim analysis, the OS data were not mature (35% of patients had died); the median follow up time was 37 months for both the rucaparib and placebo arms.
NR: Not reached.

Figure 1. Kaplan-Meier Curves of Progression-Free Survival in ATHENA as Assessed by Investigator: ITT Population



	At risk (events)							
Rubraca	427 (0)	351 (57)	245 (149)	190 (193)	114 (214)	42 (226)	7 (230)	0 (230)
Placebo	111 (0)	72 (34)	42 (61)	31 (69)	14 (76)	5 (78)	1 (78)	0 (78)

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



	At risk (events)							
Rubraca	185 (0)	165 (12)	127 (46)	100 (66)	59 (74)	22 (79)	3 (80)	0 (80)
Placebo	49 (0)	35 (13)	22 (25)	18 (28)	8 (30)	2 (31)	0 (31)	

Subgroup analysis (PFS investigator assessment)

Within the HRD Population, a hazard ratio of 0.40 (95% CI [0.21, 0.75]) was observed in the subgroup of patients with a tBRCA mutation (n=115). In the subgroup of non-tBRCA LOH^{high} (n=119), a hazard ratio of 0.58 (95% CI [0.33, 1.01]). In the HRD-negative subgroup (n=238), a hazard ratio of 0.65 (95% CI [0.45, 0.95]) was observed.

Maintenance treatment of recurrent ovarian cancer

The efficacy of rucaparib was investigated in ARIEL3, a double-blind, multicentre clinical trial in which 564 patients with recurrent EOC, FTC or PPC who were in response to platinum-based chemotherapy were randomised (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 and their cancer antigen 125 (CA-125) was below the upper limit of normal (ULN). Patients were randomised within 8 weeks of completion of platinum chemotherapy and no intervening maintenance treatment was permitted. Patients could not have received prior rucaparib or other PARP inhibitor therapy. Randomisation was stratified by best response to last platinum therapy (complete or partial), time to progression following the penultimate platinum therapy (6 to ≤ 12 months and > 12 months), and tumour biomarker status (tBRCA, non-BRCA homologous recombination deficiency [nbHRD] and biomarker negative).

The primary efficacy outcome was invPFS evaluated according to RECIST, version 1.1 (v1.1). PFS assessed by blinded independent radiology review (IRR) was a key secondary efficacy outcome. Secondary efficacy endpoints included overall survival (OS).

The mean age was 61 years (range: 36 to 85 years); most of the patients were White (80%); and all had an ECOG performance status of 0 or 1. The primary tumour in most patients was ovarian (84%); most patients (95%) had serous histology and 4% of patients reported endometrioid histology. All patients had received at least two prior platinum-based chemotherapies (range: 2 to 6) and 28% of patients had received at least three prior platinum-based chemotherapies. A total of 32% of patients were in complete response (CR) to their most recent therapy. The progression-free interval to penultimate platinum therapy was 6-12 months in 39% of patients and > 12 months in 61%. Prior bevacizumab therapy was reported for 22% of patients who received rucaparib and 23% of patients who received placebo. Demographics, baseline disease characteristics, and prior treatment history were generally well balanced between the rucaparib and placebo arms.

None of the patients had received prior treatment with a PARP inhibitor. As such, efficacy of Rubraca in patients who have received prior treatment with a PARP inhibitor in the maintenance setting, has not been investigated and cannot be extrapolated from the available data.

Tumour tissue samples for all of the patients (N=564) were tested centrally to determine HRD positive status (as defined by the presence of a deleterious tumour BRCA [tBRCA] mutation or high genomic loss of heterozygosity). Blood samples for 94% (186/196) of the tBRCA patients were evaluated using a central blood germline BRCA (gBRCA) test. Based on these results, 70% (130/186) of the tBRCA patients had a gBRCA mutation and 30% (56/186) had a somatic BRCA mutation.

The ARIEL3 study met its primary endpoint and demonstrated a statistically significant improvement in invPFS for patients randomised to rucaparib as compared with placebo in the ITT population and in the HRD and tBRCA groups. IRR- assessment for the ITT population supported the primary endpoint. PFS results are summarised in Table 5 and Figure 3.

Table 5. ARIEL3 Efficacy Results (Summary of Primary Objective Outcome: PFS)

Parameter	Investigator Assessment		IRR	
	Rucaparib	**Placebo**	**Rucaparib**	**Placebo**
ITT population [a]				
Patients, n	375	189	375	189
PFS events, n (%)	234 (62%)	167 (88%)	165 (44%)	133 (70%)
PFS, median in months (95% CI)	10.8 (8.3, 11.4)	5.4 (5.3-5.5)	13.7 (11.0, 19.1)	5.4 (5.1, 5.5)
HR (95% CI)	0.36 (0.30, 0.45)		0.35 (0.28, 0.45)	
p-value [b]	< 0.0001		< 0.0001	
HRD Group [c]				
Patients, n	236	118	236	118
PFS events, n (%)	134 (57%)	101 (86%)	90 (38%)	74 (63%)
PFS, median in months (95% CI)	13.6 (10.9, 16.2)	5.4 (5.1, 5.6)	22.9 (16.2, NA)	5.5 (5.1, 7.4)
HR (95% CI)	0.32 (0.24, 0.42)		0.34 (0.24, 0.47)	
p-value [b]	< 0.0001		< 0.0001	
tBRCA Group [d]				
Patients, n	130	66	130	66
PFS events, n (%)	67 (52%)	56 (85%)	42 (32%)	42 (64%)
PFS, median in months (95% CI)	16.6 (13.4, 22.9)	5.4 (3.4, 6.7)	26.8 (19.2, NA)	5.4 (4.9, 8.1)
HR (95% CI)	0.23 (0.16, 0.34)		0.20 (0.13, 0.32)	
p-value [b]	< 0.0001		< 0.0001	
nonBRCA LOH+ Group				
Patients, n	106	52	106	52
PFS events, n (%)	67 (63%)	45 (87%)	48 (45%)	32 (62%)
PFS, median in months (95% CI)	9.7 (7.9, 13.1)	5.4 (4.1, 5.7)	11.1 (8.2, NA)	5.6 (2.9, 8.2)
HR (95% CI)	0.44 (0.29, 0.66)		0.554 (0.35, 0.89)	
p-value [b]	< 0.0001		0.0135	
nonBRCA LOH- Group				
Patients, n	107	54	107	54
PFS events, n (%)	81 (73%)	50 (93%)	63 (59%)	46 (85%)
PFS, median in months (95% CI)	6.7 (5.4, 9.1)	5.4 (5.3, 7.4)	8.2 (5.6, 10.1)	5.3 (2.8, 5.5)
HR (95% CI)	0.58 (0.40, 0.85)		0.47 (0.31, 0.71)	
p-value [b]	0.0049		0.0003	

a All randomised patients.

b Two-sided p-value

c HRD includes all patients with a deleterious germline or somatic BRCA mutation or non-tBRCA with high genomic loss of heterozygosity, as determined by the clinical trial assay (CTA).

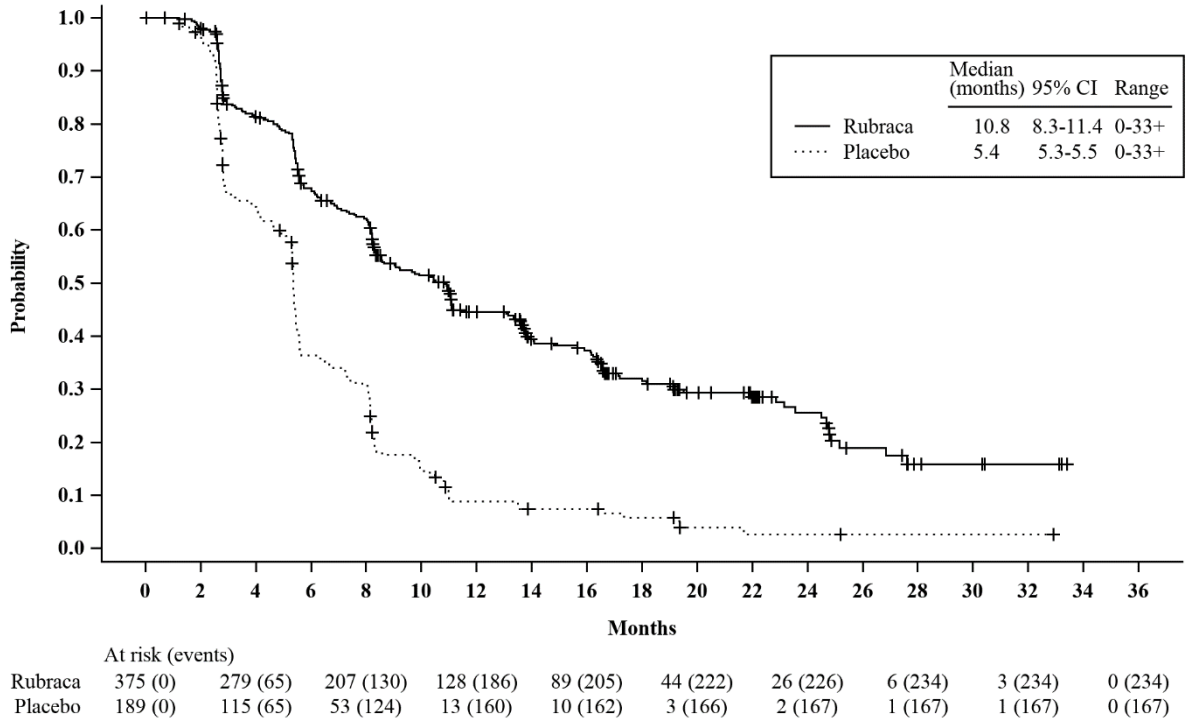
d tBRCA includes all patients with a deleterious germline or somatic BRCA mutation, as determined by the CTA.

HR: Hazard ratio. A value <1 favours rucaparib.

NA: Not Achieved

CI: Confidence interval

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



At the final OS analysis (70% maturity) the Hazard Ratio (HR) was 1.00 (95% CI: 0.81, 1.22; median 36 months for rucaparib vs 43.2 months for placebo) for the ITT population. For the HRD and tBRCA subgroups the reported HRs were 1.01 (95% CI: 0.77, 1.32; median 40.5 months for rucaparib vs 47.8 months for placebo) and 0.83 (95% CI: 0.58, 1.19; median 45.9 months for rucaparib vs 47.8 months for placebo), respectively. In an exploratory subgroup analyses of patients without a t*BRCA* mutation (non-nested, non-tBRCA subpopulations [LOH+, LOH-, LOH unknown]), the HR for OS was 1.084 (95% CI: 0.841, 1.396; median 32.2 months for rucaparib vs 38.3 months for placebo). The median survival follow-up for all patients was 77 months (6.4 years) with a range of 2 days to 93 months (7.6 years).

At the time of the final analysis, 89% of patients in the placebo arm had received at least one subsequent treatment, of whom 46% received a PARP inhibitor. In the rucaparib arm, 78% of patients had received at least one subsequent treatment.

Cardiac electrophysiology

Concentration-QTcF prolongation analysis was conducted using data from 54 patients with a solid tumour administered continuous rucaparib at doses ranging from 40 mg once daily to 840 mg twice daily (1.4 times the approved recommended dose). At the predicted median steady-state C_{max} following 600 mg rucaparib twice daily, the projected QTcF increase from baseline was 11.5 msec (90% CI: 8.77 to 14.2 msec). Thus, the risk for clinically significant QTcF increase from baseline (i.e. > 20 msec) is low.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Rubraca in all subsets of the paediatric population in ovarian cancer (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Plasma exposures of rucaparib, as measured by C_{max} and AUC, were approximately dose proportional

at evaluated doses (40 to 500 mg daily, 240 to 840 mg twice a day). Steady state was achieved after 1 week of dosing. Following repeated twice daily dosing, the accumulation based on AUC ranged from 3.5 to 6.2 fold.

Absorption

In patients with cancer following rucaparib 600 mg taken twice daily, the mean steady-state C_{max} was 1940 ng/mL and AUC_{0-12h} was 16900 h·ng/mL with T_{max} of 1.9 hours. The mean absolute oral bioavailability following a single oral dose of 12 to 120 mg rucaparib was 36%. The absolute oral bioavailability at 600 mg has not been determined. In patients with cancer following a high-fat meal, the C_{max} increased by 20%, the AUC_{0-24h} increased by 38%, and the T_{max} was delayed by 2.5 hours, as compared with dosing under fasted conditions. The food effect on PK was not considered clinically significant. Rubraca can be administered with or without food.

Distribution

The *in vitro* protein binding of rucaparib is 70.2% in human plasma at therapeutic concentration levels. Rucaparib preferentially distributed to red blood cells with a blood-to-plasma concentration ratio of 1.83. In patients with cancer, 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.

Biotransformation

In vitro, rucaparib is metabolised primarily by CYP2D6, and to a lesser extent by CYP1A2, and CYP3A4. In a population PK analysis, no clinically relevant PK differences were observed among patients with different CYP2D6 phenotypes (including poor metabolizers, n=9; intermediate metabolizers, n=71; normal metabolizers, n=76; and ultra-rapid metabolizers, n=4) or patients with different CYP1A2 phenotypes (including normal metabolizers, n=28; hyperinducers, n=136). The results should be interpreted with caution due to the limited representation of some subgroup phenotypes.

Following administration of a single oral dose of [^{14}C]-rucaparib to patients with solid tumours, unchanged rucaparib accounted for 64.0% of the radioactivity in plasma. Oxidation, N-demethylation, N-methylation, glucuronidation, and N-formylation were the major metabolic pathways for rucaparib. The most abundant metabolite was M324, an oxidative deamination product of rucaparib, accounting for 18.6% of the radioactivity in plasma. *In vitro*, M324 was at least 30 fold less potent than rucaparib against PARP-1, PARP-2, and PARP-3. Other minor metabolites accounted for 13.8% of the radioactivity in plasma. Rucaparib accounted for 44.9% and 94.9% of radioactivity in urine and faeces, respectively; while M324 accounted for 50.0% and 5.1% of radioactivity in urine and faeces, respectively.

Elimination

The clearance ranged from 13.9 to 18.4 L/hour, following a single intravenous dose of rucaparib 12 mg to 40 mg. Following administration of a single oral dose of [^{14}C]-rucaparib 600 mg to patients, the overall mean recovery of radioactivity was 89.3%, with a mean recovery of 71.9% in faeces and 17.4% in urine by 288 hours post dose. Ninety percent of the observed faecal recovery was achieved within 168 hours postdose. The mean half-life ($t_{1/2}$) of rucaparib was 25.9 hours.

Medicinal product interactions

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 OAPT1B1 and OATP1B3. Effect of P-gp and BCRP inhibitors on rucaparib PK cannot be ruled out.

In vitro, 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.

In vitro, rucaparib is a potent inhibitor of MATE1 and MATE2-K, a moderate inhibitor of OCT1, and a weak inhibitor of OCT2. At clinical exposures, rucaparib did not inhibit bile salt export pump (BSEP), OATP1B1, OATP1B3, OAT1 and OAT3. Inhibition of MRP4 by rucaparib cannot be fully ruled out at clinical exposures. No interaction with MRP2 or MRP3 was observed *in vitro* at the clinical exposure of rucaparib, however, mild bi-phasic activation and inhibition of MRP2 and concentration dependent inhibition of MRP3 were observed at concentrations higher than the observed plasma C_{max} of rucaparib. The clinical relevance of MRP2 and MRP3 interaction in the gut is not known. *In vitro*, rucaparib is an inhibitor of the BCRP and P-gp efflux transporters. No significant P-gp inhibition was observed *in vivo* (section 4.5).

Population PK analysis suggested that concomitant use of PPIs is unlikely to have clinically meaningful impact on rucaparib PK. A firm conclusion cannot be made regarding the effect of co-administration of rucaparib and PPIs because dose level and time of administration have not been documented in detail for the PPIs.

Pharmacokinetics in specific populations

Age, race, and body weight
Based on population PK analysis, no clinically significant relationships were identified between predicted steady-state exposure and patient's age, race, and body weight. Patients included in the population PK study were aged 21 to 86 years (58% < 65 years, 31% 65-74 years, and 11% > 75 years), 82% were Caucasian, and had body weights between 41 and 171 kg (73% had body weight > 60 kg).

Hepatic impairment
A population PK analysis was performed to evaluate the effect of hepatic impairment on the clearance of rucaparib in patients receiving rucaparib 600 mg twice daily. No clinically important differences were observed between 34 patients with mild hepatic impairment (total bilirubin ≤ ULN and AST > ULN or total bilirubin > 1.0 to 1.5 times ULN and any AST) and 337 patients with normal hepatic function. In a study evaluating the pharmacokinetics of rucaparib in patients with hepatic impairment, patients with moderate hepatic impairment (N=8, National Cancer Institute - Organ Dysfunction Working Group criteria; total bilirubin > 1.5 - ≤ 3 times ULN) had a 45% higher AUC of rucaparib following a single dose of 600 mg compared to patients with normal hepatic function (N=8). C_{max} or T_{max} were similar between the groups. No data are available for patients with severe hepatic impairment (see section 4.2).

Renal impairment
No formal studies of rucaparib in patients with renal impairment have been conducted. A population PK analysis was performed to evaluate the effect of renal impairment on the clearance of rucaparib in patients receiving rucaparib 600 mg twice daily. Patients with mild renal impairment (N=149; CLcr between 60 and 89 mL/min, as estimated by the Cockcroft-Gault method) and those with moderate renal impairment (N=76; CLcr between 30 and 59 mL/min) showed approximately 15% and 33% higher steady-state AUC, respectively, compared to patients with normal renal function (N=147; 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 (see section 4.2).

5.3 Preclinical safety data

General toxicology

The findings in non-clinical toxicology studies performed with oral rucaparib were generally consistent with the adverse events observed in clinical studies. In repeat-dose toxicity studies of up to 3 months duration in rats and dogs, the target organs were the gastrointestinal, haematopoietic, and lymphopoietic systems. These findings occurred at exposures below those observed in patients treated at the recommended dose, and were largely reversible within 4 weeks of cessation of dosing. *In vitro*,

the IC_{50} of rucaparib against the human ether-à-go-go related gene (hERG) was 22.6 μM, which is approximately 13-fold higher than the C_{max} in patients at the recommended dose.

Intravenous administration of rucaparib in the rat and dog induced cardiac effects at a high C_{max} (5.4 to 7.3-fold higher than patients), but not at a lower C_{max} (1.3 to 3.8-fold higher than patients). No cardiac effects were observed with oral dosing of rucaparib in repeat-dose toxicology studies at a rucaparib C_{max} comparable to that observed in patients. Although no cardiac effects were observed following oral dosing, based on the findings in the intravenous studies and safety margins, cardiac effects in patients cannot be excluded when rucaparib is given orally.

Carcinogenicity

Carcinogenicity studies have not been performed with rucaparib.

Genotoxicity

Rucaparib was not mutagenic in a bacterial reverse mutation (Ames) assay. Rucaparib induced structural chromosomal aberrations in the *in vitro* human lymphocyte chromosomal aberration assay.

Reproductive toxicology

In an embryo-foetal development study in rats, rucaparib was associated with post-implantation loss at exposures of approximately 0.04 times the human AUC at the recommended dose.

Fertility studies have not been conducted with rucaparib. No effects on male and female fertility were observed in 3-month general toxicology studies in rats and dogs at exposures of 0.09 to 0.3 times the human AUC at the recommended dose. A potential risk cannot be ruled out based on the safety margin observed. In addition, according to its mechanism of action rucaparib may have the potential to impair fertility in humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Microcrystalline cellulose
Sodium starch glycolate (Type A)
Colloidal anhydrous silica
Magnesium stearate

Rubraca 200 mg film-coated tablets

Tablet coating
Polyvinyl alcohol (E1203)
Titanium dioxide (E171)
Macrogol 4000 (E1521)
Talc (E553b)
Brilliant blue FCF aluminium lake (E133)
Indigo carmine aluminium lake (E132)

Rubraca 250 mg film-coated tablets

Tablet coating
Polyvinyl alcohol (E1203)

Titanium dioxide (E171)
Macrogol 4000 (E1521)
Talc (E553b)

Rubraca 300 mg film-coated tablets

Tablet coating
Polyvinyl alcohol (E1203)
Titanium dioxide (E171)
Macrogol 4000 (E1521)
Talc (E553b)
Iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

HDPE bottle, with a polypropylene (PP) induction seal closure, containing 60 tablets.

The following pack sizes are available:
- 1 carton with 1 bottle (60 film-coated tablets)
- 1 carton with 2 bottles (120 film-coated tablets)

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

pharmaand GmbH
Taborstrasse 1
1020 Vienna
Austria

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1250/001
EU/1/17/1250/002
EU/1/17/1250/003
EU/1/17/1250/004
EU/1/17/1250/005

EU/1/17/1250/006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 24 May 2018
Date of latest renewal: 04 March 2022

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release
Almac Pharma Services Ltd
Seagoe Industrial Estate
Craigavon
County Armagh
BT63 5UA
United Kingdom

Almac Pharma Services (Ireland) Ltd
Finnabair Industrial Estate
Dundalk
County Louth
A91 P9KD
Ireland

pharmaand GmbH
Taborstrasse 1
1020 Vienna
Austria

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Obligation to conduct post-authorisation measures**

MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
PAES: In order to further investigate the efficacy of rucaparib monotherapy in the maintenance treatment of adult patients with advanced (FIGO Stages III and IV) high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy, the MAH should submit the final analysis of OS of the phase 3, randomized, double-blind, placebo controlled study CO-338-087.	30 June 2027

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Rubraca 200 mg film-coated tablets
rucaparib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains rucaparib camsylate corresponding to 200 mg rucaparib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

60 film-coated tablets
120 (2 x 60) film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

pharmaand GmbH
Taborstrasse 1
1020 Vienna
Austria

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1250/001
EU/1/17/1250/004 120 (2 x 60) tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Rubraca 200 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

Rubraca 200 mg tablets
rucaparib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains rucaparib camsylate corresponding to 200 mg rucaparib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

60 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

pharmaand GmbH
Taborstrasse 1
1020 Vienna
Austria

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1250/001
EU/1/17/1250/004 120 (2 x 60) tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Rubraca 250 mg film-coated tablets
rucaparib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains rucaparib camsylate corresponding to 250 mg rucaparib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

60 film-coated tablets
120 (2 x 60) film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

pharmaand GmbH
Taborstrasse 1
1020 Vienna
Austria

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1250/002
EU/1/17/1250/005 120 (2 x 60) tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Rubraca 250 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

Rubraca 250 mg tablets
rucaparib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains rucaparib camsylate corresponding to 250 mg rucaparib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

60 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

pharmaand GmbH
Taborstrasse 1
1020 Vienna
Austria

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1250/002
EU/1/17/1250/005 120 (2 x 60) tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Rubraca 300 mg film-coated tablets
rucaparib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains rucaparib camsylate corresponding to 300 mg rucaparib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

60 film-coated tablets
120 (2x 60) film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

pharmaand GmbH
Taborstrasse 1
1020 Vienna
Austria

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1250/003
EU/1/17/1250/006 120 (2 x 60) tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Rubraca 300 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

Rubraca 300 mg tablets
rucaparib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains rucaparib camsylate corresponding to 300 mg rucaparib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

60 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

pharmaand GmbH
Taborstrasse 1
1020 Vienna
Austria

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1250/003
EU/1/17/1250/006 120 (2 x 60) tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Rubraca 200 mg film-coated tablets
Rubraca 250 mg film-coated tablets
Rubraca 300 mg film-coated tablets
rucaparib

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Rubraca is and what it is used for

What Rubraca is and how it works
Rubraca contains the active substance rucaparib. Rubraca is an anti-cancer medicine, also known as a 'PARP (poly adenosine diphosphate-ribose polymerase) inhibitor'.

Patients with changes (mutations) in genes called BRCA are at risk of developing a number of types of cancer. Rubraca blocks an enzyme that repairs damaged DNA in the cancer cells, resulting in their death.

What Rubraca is used for
Rubraca is used to treat a type of cancer of the ovary. It is used as maintenance therapy immediately after a course of chemotherapy that has caused the tumour to shrink.

2. What you need to know before you take Rubraca

Do not take Rubraca
- if you are allergic to rucaparib or any of the other ingredients of this medicine (listed in section 6)
- if you are breast-feeding

If you are not sure, talk to your doctor, pharmacist or nurse before taking Rubraca.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before or during taking Rubraca.

Blood tests
Your doctor or nurse will perform blood tests to check your blood cell-counts:
- before treatment with Rubraca
- every month during treatment with Rubraca

This is because Rubraca can cause low blood counts of:
- red blood-cells, white blood-cells, or platelets. See section 4 for more information. The signs and symptoms of low blood cell counts include fever, infection, bruising or bleeding.
- a low blood-cell count may be a sign of a serious bone marrow problem - such as 'myelodysplastic syndrome' (MDS) or 'acute myeloid leukaemia' (AML). Your doctor may test your bone marrow to check for any problems.

Your doctor may also do weekly tests, if you have low blood cell counts for a long time. They may stop treatment with Rubraca until your blood cell counts improve.

Take care in direct sunlight
You may get sunburn more easily during treatment with Rubraca. This means you should:
- keep out of direct sunlight and not use sunbeds while you are taking Rubraca
- wear clothing that covers your head, arms and legs
- use a sunscreen and lip balm with a sun protection factor (SPF) of 50 or higher.

Symptoms you should be aware of
Talk to your doctor if you feel sick (nauseous), have been sick (vomiting) or you have had diarrhoea or abdominal pain. These may be signs and symptoms that Rubraca is affecting your stomach or bowels.

Children and adolescents
Children under 18 years of age should not be given Rubraca. This medicine has not been studied in this age group.

Other medicines and Rubraca
Tell your doctor, pharmacist or nurse if you are taking, have recently taken, or might take any other medicines. This is because Rubraca can affect the way some other medicines work. Also some other medicines can affect the way Rubraca works.

Tell your doctor, pharmacist or nurse if you are taking any of the following medicines:
- anticoagulant medicines which helps the blood flow freely, such as warfarin
- anticonvulsant medicines used to treat fits (seizures) and epilepsy - such as phenytoin
- medicines to lower blood cholesterol levels- such as rosuvastatin
- medicines to treat stomach problems - such as cisapride, omeprazole
- medicines which suppress the immune system - such as ciclosporin, sirolimus or tacrolimus
- medicines to treat migraines and headaches - such as dihydroergotamine or ergotamine
- medicines to treat severe pain - such as alfentanil or fentanyl
- medicines used to treat uncontrolled movement or mental disorders - such as pimozide
- medicines to lower blood sugar levels and treat diabetes - such as metformin
- medicines to treat irregular heartbeats - such as digoxin or quinidine
- medicines to treat allergic reactions - such as astemizole or terfenadine
- medicines used to cause sleepiness or drowsiness - such as midazolam
- medicines used to relax muscles - such as tizanidine
- medicines used to treat asthma - such as theophylline

Pregnancy, breast-feeding and contraception
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor, nurse or pharmacist for advice before taking this medicine.

<u>Pregnancy</u>
- Rubraca is not recommended during pregnancy. This is because it may harm your unborn baby.
- For women who are able to become pregnant, a pregnancy test is recommended before starting treatment with Rubraca.

Breast-feeding
- Do not breast-feed during treatment with Rubraca, and for two weeks after taking the last dose. This is because it is not known if rucaparib passes into breast milk.

Contraception
- Women who are able to become pregnant must use effective birth control (contraception):
  - during treatment with Rubraca and
  - for 6 months after taking the last dose of Rubraca.

  This is because rucaparib may affect the unborn baby.
- Talk to your doctor or pharmacist about the most effective methods of contraception.

Driving and using machines
Rubraca may affect your ability to drive or use tools or machines. Take care if you feel tired or feel sick (nauseous).

Rubraca contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

3. How to take Rubraca

Always take this medicine exactly as your doctor, pharmacist or nurse has told you. Check with your doctor, pharmacist, or nurse if you are not sure.

How much to take
- The usual recommended dose is 600 mg twice a day. This means you take a total of 1 200 mg each day. If you have certain side effects your doctor may recommend a lower dose, or temporarily stop your treatment.
- Rubraca is available as either 200 mg, 250 mg or 300 mg tablets.

Taking this medicine
- Take the tablets once in the morning and once in the evening, approximately 12 hours apart.
- You can take the tablets with or without food.
- If you are sick (vomit) after taking Rubraca, do not take an extra dose. Take your next dose at your regular time.

If you take more Rubraca than you should
If you take more tablets than you should, tell your doctor, pharmacist or nurse straight away. You may need medical help.

If you forget to take Rubraca
- If you forget to take a dose, skip the missed dose. Then take your next dose at the usual time.
- Do not take a double dose to make up for a forgotten dose.

If you stop taking Rubraca
- It is important to keep taking Rubraca every day – as long as your doctor prescribes it for you.
- Do not stop taking this medicine without talking to your doctor first.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Tell your doctor straight away if you notice any of the following side effects – you may need urgent medical treatment:

Very common (may affect more than 1 in 10 people):
- being short of breath, feeling tired, having pale skin, or fast heart beat - these may be signs of a low red blood cell count (anaemia)
- bleeding or bruising for longer than usual if you hurt yourself - these may be signs of a low blood platelet count (thrombocytopenia)
- fever or infection – these may be signs of a low white blood cell count (neutropenia)

Other side effects include:

Very common (may affect more than 1 in 10 people):
- feeling sick (nausea)
- feeling tired
- being sick (vomiting)
- pain in the stomach
- changes in the way food tastes
- abnormal blood tests - increase in levels of liver enzymes
- loss of appetite
- diarrhoea
- abnormal blood tests - increase in blood creatinine levels
- difficulty breathing
- feeling dizzy
- sunburn
- heartburn
- high cholesterol levels
- rash

Common (may affect up to 1 in 10 people):
- dehydration
- itching
- allergic reaction (e.g. swelling of the face and eyes)
- redness, swelling, and pain on the palms of the hands and, or the soles of the feet
- red patches on the skin
- blockage in the gut or bowel
- serious bone marrow problem, such as “myelodysplastic syndrome” (MDS) or “acute myeloid leukaemia” (AML) (see section 2)
- mouth sores

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Rubraca

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the bottle and the carton after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Rubraca contains

- The active substance is rucaparib.

  Rubraca 200 mg film-coated tablets: Each film-coated tablet contains rucaparib camsylate corresponding to 200 mg of rucaparib.

  Rubraca 250 mg film-coated tablets: Each film-coated tablet contains rucaparib camsylate corresponding to 250 mg of rucaparib.

  Rubraca 300 mg film-coated tablets: Each film-coated tablet contains rucaparib camsylate corresponding to 300 mg of rucaparib.

- The other ingredients are:
  - Tablet content: Microcrystalline cellulose, sodium starch glycolate (Type A), colloidal anhydrous silica and magnesium stearate.
  - Tablet coating:
    Rubraca 200 mg film-coated tablets
    Polyvinyl alcohol (E1203), titanium dioxide (E171), macrogol 4000 (E1521), talc (E553b), brilliant blue FCF aluminium lake (E133) and indigo carmine aluminium lake (E132).

    Rubraca 250 mg film-coated tablets
    Polyvinyl alcohol (E1203), titanium dioxide (E171), macrogol 4000 (E1521), and talc (E553b).

    Rubraca 300 mg film-coated tablets
    Polyvinyl alcohol (E1203), titanium dioxide (E171), macrogol 4000 (E1521), talc (E553b), and iron oxide yellow (E172).

What Rubraca looks like and contents of the pack

- Rubraca 200 mg film-coated tablets are blue, round, film-coated tablets with “C2” marked on one side.
- Rubraca 250 mg film-coated tablets are white, diamond-shaped, film-coated tablets with “C25” marked on one side.
- Rubraca 300 mg film-coated tablets are yellow, oval, film-coated tablets with “C3” marked on one side.

Rubraca is supplied in plastic bottles. Each bottle contains 60 film-coated tablets.

The following pack sizes are available:

- 1 carton with 1 bottle (60 film-coated tablets)
- 1 carton with 2 bottles (120 film-coated tablets)

Not all pack sizes may be available in your country.

Marketing Authorisation Holder and Manufacturer
pharmaand GmbH
Taborstrasse 1
1020 Vienna
Austria

Manufacturer
Almac Pharma Services Limited
Seagoe Industrial Estate,
Portadown,
Craigavon,
BT63 5UA
United Kingdom

or

Almac Pharma Services (Ireland) Ltd
Finnabair Industrial Estate
Dundalk
County Louth
A91 P9KD
Ireland

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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Tél: +33 (0)149116680

España
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België/Belgique/Belgien, България, Česká republika, Danmark, Eesti, Ελλάδα, Hrvatska, Ireland, Ísland, Κύπρος, Latvija, Lietuva, Luxembourg/Luxemburg, Magyarország, Malta, Nederland, Norge, Österreich, Polska, Portugal, România, Slovenija, Slovenská republika, Suomi/Finland, Sverige:
Tel: 0080077889944

This leaflet was last revised in

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu