Date: 13 January 2021
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

RUBRACA

International non-proprietary name: rucaparib camsylate
Pharmaceutical form: film-coated tablets
Dosage strength(s): 200 mg, 250 mg, 300 mg
Route(s) of administration: oral
Marketing Authorisation Holder: Clovis Oncology Switzerland GmbH
Marketing Authorisation No.: 67402
Decision and Decision date: approved on 26 November 2020

Note:

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

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About Swissmedic

Swissmedic is the Swiss authority responsible for the authorisation and supervision of therapeutic products. Swissmedic's activities are based on the Federal Act of 15 December 2000 (Status as of 1 January 2020) on Medicinal Products and Medical Devices (TPA, SR 812.21). The agency ensures that only high-quality, safe and effective drugs are available in Switzerland, thus making an important contribution to the protection of human health.

About the Swiss Public Assessment Report (SwissPAR)

- The SwissPAR is referred to in Article 67 para. 1 of the Therapeutic Products Act and the implementing provisions of Art. 68 para. 1 let. e of the Ordinance of 21 September 2018 on Therapeutic Products (TPO, SR 812.212.21).
- The SwissPAR provides information about the evaluation of a prescription medicine and the considerations that led Swissmedic to approve or not approve a prescription medicine submission. The report focuses on the transparent presentation of the benefit-risk profile of the medicinal product.
- A SwissPAR is produced for all human medicinal products with a new active substance and transplant products for which a decision to approve or reject an authorisation application has been issued.
- A supplementary report will be published for approved or rejected applications for an additional indication for a human medicinal product for which a SwissPAR has been published following the initial authorisation.
- The SwissPAR is written by Swissmedic and is published on the Swissmedic website. Information from the application documentation is not published if publication would disclose commercial or manufacturing secrets.
- The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.
- In addition to the actual SwissPAR, a concise version of SwissPAR that is more comprehensible to lay persons (Public Summary SwissPAR) is also published.

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, Distribution, Metabolism, Elimination
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
AUC0-24h	Area under the plasma concentration-time curve for the 24-hour dosing interval
Cmax	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
ERA	Environmental Risk Assessment
GLP	Good Laboratory Practice
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International Nonproprietary Name
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
N/A	Not applicable
NO(A)EL	No Observed (Adverse) Effect Level
PD	Pharmacodynamics
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population PK
PSP	Pediatric Study Plan (US-FDA)
RMP	Risk Management Plan
SwissPAR	Swiss Public Assessment Report
TPA	Federal Act of 15 December 2000 (Status as of 1 January 2020) on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 (Status as of 1 April 2020) on Therapeutic Products (SR 812.212.21)

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

New Active Substance status
The applicant requested the status of a new active entity for the active substance rucaparib camsylate of the medicinal product mentioned above.

Orphan drug status
The applicant requested Orphan Drug Status in accordance with Article 4 a^{decies} no. 1 of the TPA.
The Orphan Status was granted on 7 March 2019.

Authorisation human medical product under Art. 13 TPA
The applicant requested a reduced assessment procedure in accordance with Art. 13 TPA.

2.2 Indication and Dosage

2.2.1 Requested Indication[1]

The applicant withdrew part of the initially claimed indication in ovarian cancer incl. fallopian tube cancer and primary peritoneal cancer.

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

2.2.2 Approved Indication

Rubraca is indicated for the maintenance therapy of adult patients with advanced, platinum-sensitive, relapsed, high-grade serous ovarian, fallopian tube or primary peritoneal cancer, who are in complete or partial remission following a platinum-based chemotherapy.

2.2.3 Requested Dosage

Recommended dose is 600 mg orally twice daily with or without food. Continue treatment until disease progression or unacceptable toxicity.

2.2.4 Approved Dosage

(see appendix)

[1] In this section, in view of the legal rulings on transparency and the corresponding international procedure, Swissmedic reserves the right to issue clarifications on practice in future. Given the Orphan Drug Status of the medicinal product and the fundamental importance of the question, Swissmedic has dispensed with detailed processing in this first individual case.

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2.3 Regulatory History (Milestones)

Application	26 July 2019
Formal control completed	23 August 2019
List of Questions (LoQ)	23 October 2019
Answers to LoQ	16 December 2019
2nd List of Questions (LoQ)	20 March 2020
Answers to 2nd LoQ	10 May 2020
Predecision	28 July 2020
Answers to Predecision	30 August 2020
Final Decision	26 November 2020
Decision	approval

Swissmedic has not assessed the primary data of this application and is taking over the results of the assessment of the foreign reference authority, the FDA. The current SwissPAR refers to the publicly available Assessment Report on RUBRACA, 19 December 2016, 209115 issued by the FDA.

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3 Quality Aspects

Swissmedic has not assessed the primary data relating to quality aspects of this application and is taking over the results of the assessment of the foreign reference authority FDA. The current SwissPAR relating to quality aspects refers to the publicly available Assessment Report on RUBRACA, 19 December 2016, 209115 issued by the FDA.

4 Nonclinical Aspects

Swissmedic has not assessed the primary data relating to preclinical aspects of this application and is taking over the results of the assessment of the foreign reference authority FDA. The current SwissPAR relating to preclinical aspects refers to the publicly available Assessment Report on RUBRACA, 19 December 2016, 209115 issued by the FDA.

5 Clinical and Clinical Pharmacology Aspects

Swissmedic has not assessed the primary data relating to clinical aspects of this application and is taking over the results of the assessment of the foreign reference authority FDA (for the approved indication, see chapter 2.2.2). The current SwissPAR relating to clinical aspects refers to the publicly available Assessment Report on RUBRACA, 19 December 2016, 209115 issued by the FDA.

5.1 Approved Indication and Dosage

See information for healthcare professionals in the Appendix.

6 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order to further investigate and monitor the risks as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisations.

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7 Appendix

7.1 Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to Rubraca was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the reference document, which is valid and relevant for the effective and safe use of medicinal products in Switzerland, is the information for healthcare professionals approved and authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. The Authorisation Holder is responsible for the correct translation of the text. Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

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▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

Rubraca, film-coated tablets

Composition

Active substances

Rucaparib as rucaparib camsylate

Excipients

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

Each Rubraca 200 mg film-coated tablet contains up to 1.2 mg sodium.
Each Rubraca 250 mg film-coated tablet contains up to 1.5 mg sodium.
Each Rubraca 300 mg film-coated tablet contains up to 1.8 mg sodium.

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)

Pharmaceutical form and active substance quantity per unit

Film-coated tablet containing 200 mg, 250 mg or 300 mg rucaparib as rucaparib camsylate.

Rubraca 200 mg film-coated tablet

Blue, round, immediate-release, film-coated, debossed with “C2”.

Rubraca 250 mg film-coated tablet

White, diamond, immediate-release, film-coated, debossed with “C25”.

Rubraca 300 mg film-coated tablet

Yellow, oval, immediate-release, film-coated, debossed with “C3”.

Indications/Uses

Rubraca is indicated for the maintenance therapy of adult patients with advanced, platinum-sensitive, relapsed, high-grade serous ovarian, fallopian tube or primary peritoneal cancer, who are in complete or partial remission following a platinum-based chemotherapy.

Dosage/Administration

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

Usual dosage

The recommended dose of Rubraca is 600 mg (two 300 mg tablets) taken twice daily, which corresponds to a total daily dose of 1200 mg, until disease progression or unacceptable toxicity.
If a patient misses a dose of Rubraca, the patient should resume taking Rubraca with the next scheduled dose. Vomited doses should not be replaced.

Dose adjustment following undesirable effects/interactions

To manage adverse reactions, interruption of treatment or dose reduction has to be considered.

Liver transaminase elevations (aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT)) occur early in treatment and are generally transient. Grade 1-3 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.

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)

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 x 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

Patients with impaired hepatic function

No starting dose adjustment is recommended for patients with mild hepatic impairment (total bilirubin less than or equal to upper limit of normal [ULN] and AST greater than ULN, or total bilirubin between 1.0 to 1.5 times ULN and any AST). No recommendation for starting dose adjustment is available for

patients with moderate to severe hepatic impairment (total bilirubin greater than 1.5 times ULN) due to a lack of data (see section “Pharmacokinetics”).

Patients with impaired renal function

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

Elderly patients

In clinical studies 40% (297/749) of patients with ovarian cancer treated with Rubraca were 65 years of age or older and 9% (65/749) were 75 years or older. Grade 3-4 adverse reactions occurred in 65% of patients 65 years or older and in 63% of patients 75 years or older. For patients 65 years or older, the most common Grade 3-4 adverse reactions were anaemia, fatigue/asthenia, and ALT/AST increase. No major differences in safety were observed between these patients and younger patients for the maintenance treatment of recurrent ovarian cancer or for the treatment of BRCA-mutated ovarian cancer after two or more chemotherapies.

Children and adolescents

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

Mode 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 “Pharmacokinetics”).

Contraindications

Hypersensitivity to the active substance or any of the excipients listed under Composition.

Warnings and precautions

Efficacy of Rubraca as treatment for relapsed or progressive EOC, FTC, or PPC has not been investigated in patients who have received prior treatment with a PARP inhibitor. Therefore, use in this patient population is not recommended.

Haematological toxicity

During treatment with rucaparib, events of myelosuppression (anaemia, neutropenia, thrombocytopenia) may be observed and are typically first observed after 8-10 weeks of treatment with rucaparib. These reactions are manageable with supportive measures 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 “Dosage/Administration”) 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 less than 1 month to approximately 28 months.

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.

Embryo-fetal toxicity

Rubraca can cause fetal harm when administered to a pregnant woman based on its mechanism of action and findings from animal studies.
In an animal reproduction study, administration of rucaparib to pregnant rats during the period of organogenesis resulted in embryo-fetal death at exposures that were 0.04 times the $AUC_{0\text{-}24h}$ in

patients receiving the recommended human dose of 600 mg twice daily. Pregnant women have to be informed of the potential risk to a fetus. Females of reproductive potential have to be advised to use effective contraception during treatment and for 6 months following the last dose of Rubraca (see sections “Pregnancy, lactation” and “Properties/Effects”).

Sodium content

This medicinal product contains less than 1 mmol sodium (23mg) per film-coated tablet, that is to say essentially ‘sodium-free’.

Interactions

Effects of Rubraca on other medicinal products

In a medicinal product interaction study in cancer patients, the effects of steady-state rucaparib at 600 mg twice daily on CYP1A2, CYP2C9, CYP2C19, CYP3A, and P-gp were evaluated with single oral doses of sensitive probes (caffeine, S-warfarin, omeprazole, midazolam, and digoxin, respectively). 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 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_{0-96h} 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 “Pharmacokinetics”). 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. Interactions between rucaparib and oral contraceptives have not been studied. Cisapride, pimozide, astemizole, terfenadine and dihydroergotamine / ergotamine are not authorised in Switzerland

P-gp substrates

Rucaparib showed no effect on C_{max} of digoxin while marginally increasing AUC_{0-72h} 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. In addition, rucaparib is an inhibitor of the BCRP with IC_{50} value suggesting potential BCRP inhibition and increased exposures of medicinal products that are BCRP substrates (e.g., rosuvastatin). 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.

Effect of other medicinal products on Rubraca

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.

Pregnancy, lactation

Pregnancy

Insufficient data available on use in pregnant patients.
Based on findings from animal studies and its mechanism of action, Rubraca can cause fetal harm when administered to pregnant women. In an animal reproduction study, administration of rucaparib to pregnant rats during organogenesis resulted in embryo-fetal death at maternal exposures that were 0.04 times the $AUC_{0\text{-}24h}$ in patients receiving the recommended dose of 600 mg twice daily (see also section “Preclinical data”).
The medicine should not be administered during pregnancy unless absolutely necessary.

Lactation

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

Women of childbearing age

Pregnancy testing is recommended for females of reproductive potential prior to initiating Rubraca. Rubraca can cause fetal harm when administered to a pregnant woman. Patients should be advised to use effective contraception during treatment and for 6 months following the last dose of rucaparib.

Effects on ability to drive and use machines

Rubraca has a 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 “Undesirable effects”).

Undesirable effects

Summary of the safety profile

The overall safety profile of rucaparib is based on data from 937 patients in clinical trials in ovarian cancer treated with rucaparib monotherapy.

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, thrombocytopenia and creatinine elevations. 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 (23%), ALT elevations (10%), fatigue/asthenia (10%), neutropenia (8%), thrombocytopenia (6%), and nausea (5%). 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 (20%), fatigue/asthenia (18%), nausea (16%), thrombocytopenia (15%), and AST/ALT elevations (10%). Adverse reactions leading to permanent discontinuation occurred in 10% of patients, with thrombocytopenia, nausea, anaemia, and fatigue/asthenia being the most frequent adverse reactions leading to permanent discontinuation.

List of adverse reactions

The undesirable effect frequency is listed by MedDRA System Organ Class (SOC) at the preferred term level. Frequencies of occurrence of undesirable effects 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 < 1/1000); very rare (< 1/10,000). Undesirable effects were graded using the Common Terminology Criteria for Adverse Events (CTCAE).

Neoplasms benign, malignant and unspecified (including cysts and polyps)
Common: Myelodysplastic syndrome / Acute myeloid leukaemia[a] (all grades; grade ≥3)
[a] MDS/AML rate is based on overall total patient population of 1321 who have received one dose of oral rucaparib.

Blood and lymphatic system disorders
Very common: Anaemia[b] (all grades: 42.2%; grade ≥3: 23.2%), Thrombocytopenia[b] (all grades: 26.1%), Neutropenia[b] (all grades: 16.2%)
Common: Leukopenia[b] (all grades; grade ≥3), Lymphopenia[b] (all grades), Thrombocytopenia[b] (grade ≥3), Neutropenia[b] (grade ≥3), Febrile neutropenia (all grades; grade ≥3)
Uncommon: Lymphopenia[b] (grade ≥3)
[b] Includes laboratory findings

Metabolism and nutrition disorders
Very common: Decreased appetite (all grades: 32.8%), Blood creatinine increased[b] (all grades: 19.9%)
Common: Decreased appetite (grade ≥3), Dehydration (all grades; grade ≥3), Hypercholesterolaemia[b]

(all grades)
Uncommon: Blood creatinine increased (grade ≥3), Hypercholesterolaemia[b] (grade ≥3)
[b] Includes laboratory findings

Nervous system disorders
Very common: Dysgeusia (all grades: 37.6%), Dizziness (all grades: 15.8%)
Uncommon: Dysgeusia (grade ≥3), Dizziness (grade ≥3)

Respiratory, thoracic and mediastinal disorders
Common: Dyspnoea (all grades)
Uncommon: Dyspnoea (grade ≥3)

Gastrointestinal disorders
Very common: Nausea (all grades: 76.9%), Vomiting (all grades: 42.4%), Diarrhoea (all grades: 32.6%); Dyspepsia (all grades: 11.1%), Abdominal pain (all grades: 41.4%)
Common: Nausea (grade ≥3), Vomiting (grade ≥3), Diarrhoea (grade ≥3), Abdominal pain (grade ≥3)
Uncommon: Dyspepsia (grade ≥3)

Hepatobiliary disorders
Very common: Alanine aminotransferase increased[b] (all grades: 34.8%), Aspartate aminotransferase increased[b] (all grades: 31.4%)
Common: Transaminases increased[b] (all grades), Alanine aminotransferase increased[b] (grade ≥3), Aspartate aminotransferase increased[b] (grade ≥3)
Uncommon: Transaminases increased[b] (grade ≥3)
[b] Includes laboratory findings

Skin and subcutaneous tissue disorders
Very common: Photosensitivity reaction (all grades: 13.3%), Rash (all grades: 10.1%)
Common: Rash maculo-papular (all grades), Palmar-plantar erythrodysaesthesia syndrome (all grades), Erythema (all grades)
Uncommon: Photosensitivity reaction (grade ≥3), Rash (grade ≥3), Rash maculo-papular (grade ≥3), Palmar-plantar erythrodysaesthesia syndrome (grade ≥3)

General disorders and administration site conditions
Very common: Fatigue[c] (all grades: 75.2%), Pyrexia (all grades: 12.7%)
Common: Fatigue[c] (grade ≥*3)*
Uncommon: Pyrexia (grade ≥3)

[c] 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 42%, 26% and 16% of patients, respectively. Thrombocytopenia and anaemia led to discontinuation in 1.8% and 2.1% of patients. Adverse reactions CTCAE Grade 3 or higher occurred in 23% (anaemia), 8% (neutropenia) and 6% (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 “Warnings and precautions”.

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 (1.3%) for all patients including during the long term safety follow up (rate is calculated based on overall safety population of 1321 patients exposed to at least one dose of oral rucaparib in all clinical studies). In the pivotal Phase 3 study (ARIEL3), the incidence of MDS/AML during therapy in patients who received rucaparib was 0.8%. Although no cases were reported during therapy in patients who received placebo, one case has been reported in a placebo-treated patient 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 “Warnings and precautions”.

Gastrointestinal toxicities

Vomiting and nausea were reported in 42% and 77% of patients, respectively, and were generally low grade (CTCAE Grade 1 to 3). Abdominal pain (combined terms abdominal pain, abdominal pain lower, abdominal pain upper) was reported in 40.1% of rucaparib-treated patients, but was also very common (33%) in placebo patients, most likely associated with underlying disease.

Photosensitivity

Photosensitivity was reported in 13% of patients as low grade skin reactions (CTCAE Grade 1 or 2), and by 2 (0.2%) patients as ≥ CTCAE Grade 3 reaction.

Increases in serum aminotransferases (AST/ALT)

Events related to increases in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were observed in 38% (all grades) and 11% (≥ 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 34.8% (all grades) and 9.9% (≥ CTCAE Grade 3) of patients, increased AST in 31.4% (all grades) and 2.8% (≥ CTCAE Grade 3) of patients and increased ALT and AST in 28.6% (all grades) and 2.1% (≥ 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 "Dosage/Administration"). 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 20% of patients within the first few weeks of treatment with rucaparib. Four (0.4%) 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 "Interactions"). These increases in serum creatinine were clinically asymptomatic.

Elderly

In patients ≥ 75 years old, frequencies of some adverse reactions increased: increased blood creatinine (32%), dizziness (20%), pruritus (15%), and memory impairment (4%) were higher than in patients < 75 years old (18%, 15%, 9% and 1%, respectively).

Patients with renal impairment

In patients with moderate renal impairment (CLcr of 30-59 mL/min), frequencies of some adverse reactions increased: Grade 3 or 4 anaemia (31%), Grade 3 or 4 thrombocytopenia (12%), and Grade 3 fatigue/asthenia (15%) were higher than in patients with mild renal impairment (CLcr > 59-80 mL/min) or normal renal function (CLcr > 80 mL/min) (21%, 5%, and 8%).

Paediatric population

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

Reporting suspected adverse reactions after authorisation

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

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.

Properties/Effects

ATC code

L01XX55

Mechanism of action

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

Pharmacodynamics

The pharmacodynamic response of rucaparib has not been characterized.

Cardiac electrophysiology

The effect of multiple doses of rucaparib on QTc interval was evaluated in an open-label single-arm study in 56 patients with solid tumors who were administered continuous doses of rucaparib ranging from 40 mg once daily (0.03 times the approved recommended dose) to 840 mg twice daily (1.4 times the approved recommended dose). The mean QTcF increase from baseline (90% confidence interval [CI]) in population pharmacokinetics estimated 95th percentile C_{max} (3019 ng/mL) at steady state of 600 mg rucaparib twice daily was 14.9 msec (11.1-18.7 msec). Thus, the risk for clinically significant QTcF increase from baseline (i.e. > 20 msec) is low.

Clinical efficacy

Maintenance treatment of platinum-sensitive recurrent ovarian cancer

The efficacy of rucaparib was investigated in ARIEL3 (NCT01968213), a double-blind, multicenter clinical trial in which 564 patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who were in response to platinum-based chemotherapy and were randomized (2:1) to receive

Rubraca tablets 600 mg orally twice daily (n=375) or placebo (n=189). Treatment was continued until disease progression or unacceptable toxicity. All patients had achieved a response (complete or partial) to their most recent platinum-based chemotherapy. Randomization was stratified by best response to last platinum (complete or partial), time to progression following the penultimate platinum therapy (6 to ≤ 12 months and > 12 months), and tumor biomarker status. The major efficacy outcome was investigator-assessed progression-free survival (PFS) evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1 (v1.1).

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

Tumour tissue samples for all of the patients (N=564) were tested centrally to determine homologous recombination deficiency (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.

ARIEL3 demonstrated a statistically significant improvement in PFS for patients randomized to rucaparib as compared with placebo in all patients, and in the HRD and tBRCA subgroups. In ARIEL3, 236 [63%] rucaparib-treated and 118 [62%] placebo-treated patients were in the HRD subgroup, and 130 [35%] rucaparib-treated and 66 [35%] placebo-treated patients were in the tBRCA subgroup. The median PFS in the BRCA subgroup was 16.6 months (95% CI 13.4–22.9) in the rucaparib group versus 5.4 months (95% CI 3.4–6.7) in the placebo group (HR 0.23 [95% CI 0.16–0.34]; p<0.0001). In the HRD subgroup the median PFS was 13.6 months (95% CI 10.9–16.2) in the rucaparib group versus 5.4 months (95% CI 5.1–5.6) in the placebo group (HR 0.32 [0.24–0.42]; p<0.0001). In the ITT population (all randomized patients), the median PFS was 10.8 months (95% 8.3–11.4) in the rucaparib group versus 5.4 months (95% CI 5.3–5.5) in the placebo group (HR 0.36 [0.30–0.45]; p<0.0001). Results from a blinded independent radiology review were consistent in ITT and across all subgroups. At the time of the analysis of PFS, OS data were not mature (with 22% of events having been reported as of the data cutoff date).

Pharmacokinetics

Absorption

The median T_{max} was 1.9 hours at the approved recommended dose. The mean absolute bioavailability of rucaparib immediate-release tablet was 36% with a range from 30% to 45%. Following a high-fat meal, the C_{max} was increased by 20% and AUC_{0-24h} was increased by 38%, and T_{max} was delayed by 2.5 hours, as compared to administration under fasted conditions (see section “Dosage/Administration”).

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.

Metabolism

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

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.

Linearity/non-linearity

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

Kinetics in specific patient groups

Rucaparib PK was assessed in patients of 21– 86 years of age (58% < 65 years, 31% 65-74 years, and 11% > 75 years) in the weight range 41 kg – 171 kg (73% with a body weight of > 60 kg) with the majority being Caucasians (82%). Based on population pharmacokinetic analyses, age, race, and body weight did not have a clinically meaningful effect on rucaparib exposure.

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.

Renal impairment

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

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.

Preclinical data

Mutagenicity

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

Carcinogenicity

Carcinogenicity studies have not been conducted with rucaparib.

Reproductive toxicity

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.

Embryo-fetal development studies

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 $AUC_{0\text{-}24h}$).

Other information

Incompatibilities

Not applicable.

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the pack.

Special precautions for storage

Do not store above 30°C.
Keep out of the reach of children.

Authorisation number

67402 (Swissmedic)

Packs

Rubraca 200mg: pack of 60 film-coated tablets [A]

Rubraca 250mg: pack of 60 film-coated tablets [A]

Rubraca 300mg: pack of 60 film-coated tablets [A]

Marketing authorisation holder

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