Olaparib (Capsule) Monotherapy

Note:

- **There are two formulations of olaparib available, olaparib tablets and capsules, which are NOT interchangeable.**
- **These formulations differ in the dosing and bioavailability of each formulation and the specific dose recommendations for each formulation should be followed.**
- **This regimen is for treatment with olaparib capsules only**

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Maintenance treatment of adult patients with platinum -sensitive relapsed *BRCA*-mutated (germline and/or somatic) -			
• high grade serous epithelial ovarian cancer	C56	00341a	CDS 01/11/2017
• fallopian tube cancer	C48	00341b	CDS 01/11/2017
• primary peritoneal cancer	C57	00341c	CDS 01/11/2017
-who are in response (complete response or partial response) to platinum-based chemotherapy.			

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

Olaparib is taken twice daily continuously until disease progression or unacceptable toxicity develops.

Drug	Dose	Route	Cycle
Olaparib (capsule)	400mg Twice Daily	PO	Continuous
Olaparib capsules cannot be substituted with olaparib tablets on a milligram-to-milligram basis due to differences in the dosing and bioavailability of each formulation			
Patients should take olaparib at least one hour after food, and refrain from eating, preferably for up to 2 hours afterwards.			
If a patient misses a dose of olaparib, they should take their next normal dose at its scheduled time.			

ELIGIBILITY:

- Indications as above
- BRCA mutation (germline or somatic) as demonstrated by an accurate and validated test method
- ECOG status 0-2
- Completed their previous platinum containing chemotherapy regimen in the previous 8 weeks.
- Completed at least two courses of platinum-based chemotherapy.

- The cancer is required to be platinum-sensitive (an objective response to the penultimate platinum-based regimen of more than six months) and the most recent regimen must have induced an objective response. (Either partial (PR) or complete response (CR))
- Patients' pre-treatment CA-125 value is within the upper limit of normal, or if greater, then a repeated level after seven days increased by less than 15% of the first measurement.
- Life expectancy at least 16 weeks

EXCLUSIONS:

- Hypersensitivity to olaparib, or any of the excipients.
- Hepatic impairment (bilirubin > 1.5 xULN)
- Breast-feeding during treatment and 1 month after the last dose
- Pregnancy

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist.

TESTS:

Baseline tests:

- FBC, liver and renal profile
- A pregnancy test should be performed on all premenopausal women prior to treatment.

Regular tests:

- FBC, liver and renal profile every 4 weeks for the first 12 months and then as clinically indicated
- Consider regular pregnancy testing as indicated

Disease monitoring:

Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant
- Treatment may be interrupted to manage adverse reactions such as nausea, vomiting, diarrhoea, and anaemia. Dose reduction can be considered in these cases (Table 1).

Table1: Dose reduction for adverse events

Dose Level	Dose Recommendation	Total Daily Dose
Starting dose	400mg Twice Daily	800mg
Dose -1	200mg Twice Daily	400mg
Dose -2	100mg Twice Daily	200mg

Renal and Hepatic Impairment:

Table 2: Dose modification of olaparib in renal and hepatic impairment

Renal Impairment		Hepatic Impairment	
CrCl (ml/min)	**Dose**		**Dose**
51-80	400mg Twice Daily	**Mild**[+]	100% dose
31-50	300mg Twice Daily	**Moderate**[+]	100% dose
≤30	Not recommended*	**Severe**[+]	Not recommended as safety and pharmacokinetics have not been studied in these patients.

*Olaparib may only be used in patients with severe renal impairment if the benefit outweighs the potential risk, and the patient should be carefully monitored for renal function and adverse events.
[+]Mild; Child-Pugh A, Moderate; Child-Pugh B, Severe; Child-Pugh C

Dose adjustments for co-administration with CYP3A inhibitors

- Concomitant use of strong and moderate CYP3A inhibitors is not recommended and alternative agents should be considered.
- If a strong or moderate CYP3A inhibitor must be co-administered the recommended dose of olaparib is shown in Table 3 below

Table 3: Dose modification of olaparib when co-administered with strong or moderate CYP3A inhibitors

Class of CYP3A inhibitor	Dose Recommendation	Total Daily Dose
Strong CYP3A inhibitor	150mg Twice Daily	300mg
Moderate CYP3A inhibitor	200mg Twice Daily	400mg

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: Moderate to High **(Refer to local policy).**

PREMEDICATIONS:

Consider the use of

- Anti-emetics (**Refer to local policy).**
- Proton Pump Inhibitor (**Refer to local policy).**

OTHER SUPPORTIVE CARE:

Women of childbearing potential must use effective contraception during therapy and for 1 month after receiving the last dose of olaparib. Due to the potential interaction of olaparib with hormonal contraception an additional non-hormonal contraceptive method and regular pregnancy tests should be considered during treatment

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

This medicinal product is subject to additional monitoring. Healthcare professionals are asked to report any suspected adverse reactions*The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details*.

- **Haematological toxicity:** Haematological toxicity has been reported in patients treated with olaparib, including clinical diagnoses and/or laboratory findings of generally mild or moderate (CTCAE grade 1 or 2) anaemia, neutropenia, thrombocytopenia and lymphopenia. Patients should not start treatment with olaparib until they have recovered from haematological toxicity caused by previous anticancer therapy (haemoglobin, platelet, and neutrophil levels should be within normal range or CTCAE grade 1).
  If a patient develops severe haematological toxicity or blood transfusion dependence, treatment with olaparib should be interrupted and appropriate haematological testing should be initiated. If the blood parameters remain clinically abnormal after 4 weeks of olaparib dose interruption, bone marrow analysis and/or blood cytogenetic analysis are recommended.
- **Myelodysplastic syndrome/Acute Myeloid Leukaemia:** Myelodysplastic syndrome/Acute Myeloid Leukaemia (MDS/AML) have been reported in a small number of patients who received olaparib alone or in combination with other anti-cancer drugs; the majority of cases have been fatal. The duration of therapy with olaparib in patients who developed MDS/AML varied from < 6 months to > 2 years. If MDS and/or AML are confirmed while on treatment with olaparib, it is recommended that the patient be treated appropriately. If additional anticancer therapy is recommended, olaparib should be discontinued and not given in combination with other anticancer therapy.
- **Pneumonitis:** Pneumonitis has been reported in a small number of patients receiving olaparib, and some reports have been fatal. The reports of pneumonitis had no consistent clinical pattern and were confounded by a number of pre-disposing factors (cancer and/or metastases in lungs, underlying pulmonary disease, smoking history, and/or previous chemotherapy and radiotherapy). If patients present with new or worsening respiratory symptoms such as dyspnoea, cough and fever, or a radiological abnormality occurs, olaparib treatment should be interrupted and prompt investigation initiated. If pneumonitis is confirmed, olaparib treatment should be discontinued and the patient treated appropriately.
- **Embryofoetal toxicity:** Based on its mechanism of action (PARP inhibition), olaparib could cause foetal harm when administered to a pregnant woman. Nonclinical studies in rats have shown that olaparib causes adverse effects on embryofoetal survival and induces major foetal malformations at exposures below those expected at the recommended human dose of 400mg twice daily.
- **Folate deficiency:** Case reports of folate deficiency have been published (3,4). Physicans should monitor levels and treat accordingly. An international study to evaluate the serum folate levels in patients treated with olaparib is ongoing (5).

DRUG INTERACTIONS:

- No formal drug interaction studies have been performed
- Clinical studies of olaparib in combination with other anticancer medicinal products, including DNA damaging agents, indicate a potentiation and prolongation of myelosuppressive toxicity. The recommended olaparib monotherapy dose is not suitable for combination with other anticancer medicinal products.
- Olaparib co-administration with strong or moderate CYP3A inhibitors is not recommended
  - If a strong or moderate CYP3A inhibitor must be co-administered, the dose of olaparib should be reduced as per Table 3 above.

- Olaparib co-administration with strong CYP3A inducers is not recommended. In the event that a patient already receiving olaparib requires treatment with a strong CYP3A inducer, the prescriber should be aware that the efficacy of olaparib may be substantially reduced.
- Olaparib inhibits CYP3A4 *in vitro* and is predicted to be a mild CYP3A inhibitor *in vivo*. Therefore, caution should be exercised when sensitive CYP3A substrates or substrates with a narrow therapeutic margin are combined with olaparib.
    - Appropriate clinical monitoring is recommended for patients receiving CYP3A substrates with a narrow therapeutic margin concomitantly with olaparib.
- Induction of CYP1A2, 2B6 and 3A4 has been shown in vitro with CYP2B6 being most likely to be induced to a clinically relevant extent. The potential for olaparib to induce CYP2C9, CYP2C19 and P-gp can also not be excluded. Therefore, olaparib upon co-administration may reduce the exposure to substrates of these metabolic enzymes and transport protein. The efficacy of hormonal contraceptives may be reduced if co-administered with olaparib.
- *In vitro*, olaparib inhibits the efflux transporter P-gp, therefore it cannot be excluded that olaparib may cause clinically relevant drug interactions with substrates of P-gp.
    - Appropriate clinical monitoring is recommended for patients receiving this type of medicinal product concomitantly
- In vitro, olaparib has been shown to be an inhibitor of OATP1B1, OCT1, OCT2, OAT3, MATE1 and MATE2K. It cannot be excluded that olaparib may increase the exposure to substrates of OATP1B1 (e.g. bosentan, glibenclamide, repaglinide, statins, and valsartan), OCT1 (e.g. metformin), OCT2 (e.g. serum creatinine), OAT3 (e.g. furosemide and methotrexate), MATE1 (e.g. metformin) and MATE2K (e.g. metformin). In particular, caution should be exercised if olaparib is administered in combination with any statin.
- Combination of olaparib with vaccines or immunosuppressant agents has not been studied. Therefore, caution should be taken if these drugs are co-administered with olaparib and patients should be closely monitored.
- Current drug interaction databases should be consulted for more information.

ATC CODE:

Olaparib - L01XX46

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Version	Date	Amendment	Approved By
1	08/05/2017		Prof Seamus O'Reilly
2	01/11/2017	Updated reimbursement status	NCCP
3	19/11/2019	Biennial review. Updated hepatic dose modifications, dose adjustments, adverse events for folate deficiency and emetogenic potential.	Prof Seamus O'Reilly
4	23/10/2020	Updated drug interaction information. Added statement clarifying different posology/bioavailability of tablet and capsule formulations	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.