Indication	For the treatment of metastatic hormone-relapsed (castrate-resistant) prostate cancer in patients who are treatment naïve to androgen receptor inhibitors and in whom chemotherapy is not yet clinically indicated or appropriate. NB: the patient should not have previously received an androgen receptor inhibitor such as enzalutamide, abiraterone, apalutamide or darolutamide at any place in the prostate cancer treatment path-way except in the case of patients who received androgen receptor inhibitor therapy for hormone-sensitive disease and stopped this treatment more than 12 months prior, without PSA progression or evidence of clinical or radiological progressive disease at the time such androgen receptor inhibitor therapy was discontinued.
Treatment Intent	Palliative
Frequency and number of cycles	Repeat every 28 days. Continue until disease progression, unacceptable toxicity or patient choice to discontinue treatment, whichever is the sooner. A formal medical review as to whether treatment should continue or not will be scheduled to occur by the start of the 3rd cycle of treatment.
Monitoring Parameters pre-treatment	• **Virology screening:** All new patients referred for systemic anti-cancer treatment should be screened for hepatitis B and C and the result reviewed prior to the start of treatment. Patients not previously tested who are starting a new line of treatment, should also be screened for hepatitis B and C. Further virology screening will be performed following individual risk assessment and clinician discretion. • Monitor FBC and U&E's prior to each cycle for 12 months and then every 3 months if clinically appropriate. • Before the start of treatment PLT >/=75, neuts >/=1.5, Hb >/=10, otherwise d/w consultant. • Monitor LFTs every 2 weeks for first 3 months then monthly for 9 months and then every 3 months thereafter if clinically indicated. • Blood pressure, serum potassium and fluid retention should be monitored before treatment and at least monthly thereafter. In patients at high risk of congestive heart failure monitoring should be 2 weekly for the first 3 months of treatment, then if clinically stable monthly thereafter. • Use with caution if history of cardiovascular disease (before treatment hypertension must be controlled and hypokalaemia corrected, consider maintaining potassium levels at >/=4mmol/L during treatment). New patients with cardiac failure should have an ECHO (transthoracic echocardiogram to measure Left Ventricular Ejection Fraction) before starting treatment. • **Hepatic impairment:** • **Olaparib:** No dose adjustment required in mild or moderate hepatic impairment (Child-Pugh classification A or B). Not recommended for use in patients with severe hepatic impairment (Child-Pugh classification C). • **Abiraterone:** no dose adjustment in pre-existing mild (Child-Pugh A) impairment. Limited data available in moderate (Child-Pugh B) impairment, to be prescribed at clinician's decision. Not to be used in severe hepatic impairment. • **Renal impairment:** • **Olaparib:** No dose reduction required in mild impairment (CrCL 51-80ml/min), in moderate impairment (CrCl 31-50 ml/min) a dose reduction of 200mg twice a day is recommended. Not recommended to be used in patients with severe or end stage renal disease (CrCl</=30ml/min), clinician's decision. • **Abiraterone:** Use with caution in severe renal impairment.

- **Haematological toxicity guidance for olaparib:**
  - If neuts <1 and/or PLT <50 and/or Hb <80 delay until neuts >/=1.5, PLT >/=75 and Hb >/= 90 and consider dose reduction.
  - If reoccurrence interrupt and dose reduce.
  - If severe haematological toxicity or blood transfusion dependence occurs, treatment with olaparib should be interrupted and appropriate haematological testing should be initiated.
  - Abiraterone may continue if olaparib is withheld due to haematological toxicity.
- **Management of adverse reactions and dose adjustments:**
- For patients who develop Grade >/= 3 toxicities including hypertension, hypokalaemia, oedema and other non-mineralocorticoid toxicities, treatment should be withheld and appropriate medical management should be instituted. Treatment should not be reinitiated until symptoms of the toxicity have resolved to Grade 1 or baseline.
- **Hepatotoxicity and hepatic impairment:**
  - Cases of hepatotoxicity have been reported with olaparib and abiraterone.
  - If increase in ALT>5x ULN, discontinue treatment and all other concomitant medications that are potentially hepatotoxic. Re-treatment may take place only after return of liver function tests to the patient's baseline, and at the reduced dose level of abiraterone 500mg once a day and olaparib 250mg bd (or 200mg bd if already reduced) with serum transaminases monitored at least every two weeks for three months and monthly thereafter. No further dose reduction is permitted; if hepatotoxicity recurs at the reduced dose treatment should be discontinued.
  - If patients develop severe hepatotoxicity (ALT 20 x ULN) discontinue treatment and do not re-treat.

  Olaparib:
  - Treatment may be interrupted to manage adverse reactions such as nausea, vomiting, diarrhoea, and anaemia and dose reduction can be considered.
  - The recommended dose reduction is to 250mg twice daily (equivalent to a total daily dose of 500 mg). If a further final dose reduction is required, then reduction to 200mg twice daily (equivalent to a total daily dose of 400 mg) is advised. NB see below for dose adjustment when co-administered with CYP3A inhibitors.
  - If patients present with new or worsening respiratory symptoms such as dyspnoea, cough and fever, or a radiological abnormality occurs, treatment with olaparib should be interrupted and prompt investigation initiated. If pneumonitis is confirmed, treatment with olaparib should be discontinued and the patient treated appropriately.
  - Monitor patients for clinical signs and symptoms of venous thrombosis and pulmonary embolism and treat as medically appropriate. Patients with a prior history of VTE may be more at risk of a further occurrence and should be monitored appropriately.

  Prednisolone: Prednisolone dose may be reduced to 5 mg od at clinicians' discretion.
- **<u>Common drug interactions (for comprehensive list refer to BNF/SPC)</u>:**
- **Olaparib:**
  - Avoid concomitant treatment with strong or moderate CYP3A inhibitors (e.g. ketoconazole, itraconazole, clarithromycin, and erythromycin). If a strong CYP3A inhibitor must be given, the recommended dose reduction is to 100mg taken twice daily. If a moderate CYP3A inhibitor must be given, the recommended dose reduction is to 150mg taken twice daily.
  - Avoid grapefruit and grapefruit juice throughout the course of treatment.
  - Co-administration with strong or moderate CYP3A inducers is not recommended. In the event that a patient requires treatment with a strong (e.g. phenytoin, rifampicin, carbamazepine) or moderate (e.g. rifabutin, efavirenz) CYP3A inducer, the prescriber should be aware that the efficacy of olaparib may be substantially reduced.

	○ Caution and appropriate monitoring when administered with sensitive CYP3A substrates or substrates with a narrow therapeutic margin (e.g. simvastatin, cisapride, and cyclosporine). ○ Co-administration may reduce the exposure to substrates of the CYP2C9, CYP2C19 and P-gp; the efficacy of some hormonal contraceptives may be reduced. ○ Olaparib may increase exposure to substrates of BCRP, OATP1B1, OCT1, OCT2, OAT3, MATE1 and MATE2K. Caution should be exercised if olaparib is administered in combination with any statin. • **Abiraterone:** ○ Caution is recommended in patients concomitantly treated with drugs known to be associated with myopathy/rhabdomyolysis (e.g. glucocorticoids, cholesterol lowering drugs, zidovudine, amiodarone, colchicine) ○ Strong inducers (e.g. phenytoin, carbamazepine, rifampicin) of CYP3A should be avoided or used with caution. ○ Dose reduction of medicines with a narrow therapeutic index metabolized by CYP2D6 (e.g. metoprolol, propranolol, venlafaxine, haloperidol, risperidone) should be considered. ○ Use with caution when given concomitantly with other medications known to prolong QT interval. ○ Avoid spironolactone, co administration with abiraterone is not recommended. ○ Hyperglycaemia/Hypoglycaemia: The risk of hypoglycaemia has been linked to co-administration with pioglitazone or repaglinide. Patients with diabetes should be advised to closely monitor their blood sugars and liaise with their diabetic team. Close monitoring for toxicity is recommended for patients taking CYP2C8 substrate with a narrow therapeutic index (e.g. pioglitazone and repaglinide). • **Missed dose:** If a patient misses a dose of olaparib, abiraterone or prednisolone they should not take the dose and take their next normal dose at its scheduled time. • **Driving:** • Olaparib: Olaparib may cause drowsiness and dizziness, patients should be made aware and advised if affected to not drive or operate machinery. • **For oral self-administration: refer to local Trust policy on oral anti-cancer medicines and supply Patient Information Leaflet.**
References	KMCC protocols URO-021 V5 and MULTI-029 V1 CDF list V1.285 accessed online. BlueTeq form accessed online 29.12.2023 SPC accessed online 28.12.2023 https://clinicaltrials.gov/study/NCT01972217

NB For funding information, refer to CDF and NICE Drugs Funding List

Repeat every 28 days

TTO	Drug	Dose	Route	Directions
Day 1	**OLAPARIB**	**300mg**	PO	BD, 12 hours apart, to be taken as continuous treatment. Do not take with grapefruit juice. Swallow whole do not crush/chew or dissolve. Available as 150mg and 100mg tablets
	Add LHRH agonists/antagonists where appropriate			
	ABIRATERONE	**1000mg**	PO	Each day continuously for 28 days. Tablets should be taken at least 1 hour before food or at least 2 hours after eating. Swallow whole with water. Available as 500mg tablets.
	PREDNISOLONE	**5mg**	PO	BD for 28 days
	Metoclopramide	10mg	PO	TDS PRN Do not take for more than 5 days continuously. Dispense 28 tablets on cycle 1, then only if specified.
	Loperamide	2mg-4mg	PO	Take 4mg initially then 2mg after each loose stool when required max 16mg a day. Dispense 1 x op on cycle 1, then when required.