Talazoparib Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Talazoparib is indicated as monotherapy for the treatment of adult patients with germline BRCA1/2-mutations, who have HER2-negative locally advanced or metastatic breast cancer. Patients should have been previously treated with an anthracycline and/or a taxane in the (neo)adjuvant, locally advanced or metastatic setting unless patients were not suitable for these treatments. Patients with hormone receptor (HR)-positive breast cancer should have been treated with a prior endocrine-based therapy or be considered unsuitable for endocrine-based therapy.	C50	00605a	CDS 01/05/2021

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.

Talazoparib is given once daily until disease progression or unacceptable toxicity occurs.

Drug	Dose	Route	Diluent & Rate	Cycle
Talazoparib	1mg	PO	n/a	Continuous
If the patient vomits or misses a dose, an additional dose should not be taken. The next prescribed dose should be taken at the usual time.				
The capsules should be swallowed whole, and must not be opened or dissolved. They can be taken with or without food.				

ELIGIBILITY:

- Indication as above
- Metastatic or locally advanced, histologically documented breast cancer (absence of HER2 expression)
- Presence of deleterious or suspected deleterious germline BRCA mutations determined by a validated test method.
- Prior treatment with a taxane and/or anthracycline unless medically contraindicated
- ECOG ≤ 2
- No more than 3 prior chemotherapy-inclusive regimens for locally advanced and/or metastatic disease

EXCLUSIONS:

- Hypersensitivity to talazoparib or to any of the excipients
- Prior treatment with a PARP inhibitor
- Symptomatic central nervous system (CNS) metastases
- Leptomeningeal disease
- Breast-feeding
- Objective disease progression while receiving platinum chemotherapy administered for locally advanced or metastatic disease
- Relapse within 6 months of the last dose of prior platinum therapy in the adjuvant or neoadjuvant setting
- Active inflammatory breast cancer
- HER2 positive breast cancer
- Myocardial infarction within 6 months before randomization, symptomatic congestive heart failure (New York Heart Association [NYHA] > class II), unstable angina, or unstable cardiac arrhythmia requiring medication)

PRESCRIPTIVE AUTHORITY:

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

TESTS:

Baseline tests:

- Confirmation of deleterious or suspected deleterious germline mutations in the breast cancer susceptibility genes (*BRCA*) 1 or 2 as confirmed by a validated test method
- Confirmation of absence of HER2 expression
- FBC, renal and liver profile
- A pregnancy test should be performed on all premenopausal woman prior to treatment

Regular tests:

- FBC, renal and liver profile every 4 weeks or 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:

- To manage adverse drug reactions, interruption of treatment or dose reduction based on severity and clinical presentation should be considered
- Recommended dose reduction levels are indicated in Table 1.
- Any dose modification should be discussed with a Consultant

Table 1. Recommended dose reduction levels for toxicities

Dose level	Talazoparib daily dose (mg)
Recommended starting dose	1 mg
1st Dose Level Reduction	0.75 mg
2nd Dose Level Reduction	0.5mg
3rd Third level reduction	0.25mg

Haematological:

Table 2: Recommended dose modification of talazoparib in haematological toxicity

Parameter	Interruption criteria	Resumption criteria
Haemoglobin (g/dL)	<8	≥ 9 and resume at the next lower dose level
ANC ($x10^9$/L)	<1.0	≥ 1.5 and resume at the next lower dose level
Platelets ($x10^9$/L)	<50	≥ 75 and resume at the next lower dose level

Renal and Hepatic Impairment:

Table 3: Recommended dose modification of talazoparib in renal and hepatic impairment

Renal Impairment		Hepatic Impairment			
Cr Cl (ml/min)	**Dose**	**Bilirubin**		**AST**	**Dose**
≥ 60	100% dose	≤1 x ULN	and	> ULN	No dose adjustment is required
30 – 59	Recommended starting dose is 0.75 mg once daily	>1-1.5 x ULN	and	any	
15 - 29	Recommended starting dose is 0.5 mg once daily	>1.5-3 x ULN	and	any	
<15 or Patients requiring haemodialysis	Has not been studied / no data available	>3 x ULN	and	any	

Management of adverse events:

Table 4: Recommended dose modification of talazoparib for Adverse Events

Adverse reactions	Recommended dose modification
Non-haematologic adverse reaction Grade 3 or Grade 4	Withhold until symptoms resolve to ≤ Grade 1 and consider resuming talazoparib at next lower dose or discontinue

Dose modification: Concomitant treatment with p-glycoprotein inhibitors

- Concomitant use of strong P-gp inhibitors during treatment with talazoparib should be avoided.
- Co-administration should only be considered after careful evaluation of the potential benefits and risks.
- If co-administration with a strong P-gp inhibitor is unavoidable, the talazoparib dose should be reduced to the next lower dose.
- When the strong P-gp inhibitor is discontinued, the talazoparib dose should be increased (after 3-5 half-lives of the P-gp inhibitor) to the dose used prior to the initiation of the strong P-gp inhibitor.

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: Minimal to low (**Refer to local policy).**

PREMEDICATIONS: None

OTHER SUPPORTIVE CARE: None

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS:

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

Talazoparib is subject to additional monitoring. Healthcare professionals are asked to report any suspected adverse reactions.

- **Myelosuppression:** Myelosuppression consisting of anaemia, leucopenia/neutropenia, and/or thrombocytopenia, have been reported in patients treated with talazoparib. Talazoparib should not be started until patients have recovered from haematological toxicity caused by previous therapy (≤ Grade 1). Precautions should be taken to routinely monitor haematology parameters and signs and symptoms associated with anaemia, leucopenia/neutropenia, and/or thrombocytopenia in patients receiving talazoparib. If such events occur, dose modifications (reduction or interruption) are recommended. Supportive care with or without blood and/or platelet transfusions and/or administration of colony stimulating factors may be used as appropriate.
- **Myelodysplastic syndrome/Acute myeloid leukaemia:** Myelodysplastic syndrome/Acute Myeloid Leukaemia (MDS/AML) have been reported in patients who received poly (adenosine diphosphate-ribose) polymerase (PARP) inhibitors, including talazoparib. Overall, MDS/AML has been reported in <1% of solid tumour patients treated with talazoparib in clinical studies. Potential contributing factors for the development of MDS/AML include previous platinum-containing chemotherapy, other DNA damaging agents or radiotherapy. Complete blood counts should be obtained at baseline and monitored monthly for signs of haematologic toxicity during treatment. If MDS/AML is confirmed, talazoparib should be discontinued.
- **Embryofoetal toxicity:** Talazoparib was clastogenic in an *in vitro* chromosomal aberration assay in human peripheral blood lymphocytes and in an *in vivo* bone marrow micronucleus assay in rats but not mutagenic in Ames assay, and may cause foetal harm when administered to a pregnant woman. Pregnant women should be advised of the potential risk to the foetus.

- **Pregnancy/contraception:** Women of childbearing potential should not become pregnant while receiving talazoparib and should not be pregnant at the beginning of treatment. A pregnancy test should be performed on all women of childbearing potential prior to treatment.
    - A highly effective method of contraception is required for female patients during treatment with talazoparib, and for at least 7 months after completing therapy. Since the use of hormonal contraception is not recommended in patients with breast cancer, two non-hormonal and complementary contraception methods should be used.
    - Male patients with female partners of reproductive potential or pregnant partners should be advised to use effective contraception (even after vasectomy), during treatment with talazoparib and for at least 4 months after the final dose.
- **Breast-feeding:** It is unknown whether talazoparib is excreted in human breast milk. A risk to breast-fed children cannot be excluded and therefore breast-feeding is not recommended during treatment with talazoparib and for at least 1 month after the final dose.
- **Fertility:** There is no information on fertility in patients. Based on non-clinical findings in testes (partially reversible) and ovary (reversible), talazoparib may impair fertility in males of reproductive potential.

DRUG INTERACTIONS:

- Concomitant use of strong P-gp inhibitors should be avoided. If co-administration with a strong P-gp inhibitor is unavoidable, the talazoparib dose should be reduced.
- Concomitant use of strong BCRP inhibitors should be avoided. If co-administration of strong BCRP inhibitors cannot be avoided, patient should be monitored for potential increased adverse reactions.
- Current drug interaction databases should be consulted for more information.

REFERENCES:

1. Litton JK et al. Talazoparib in Patients with Advanced Breast Cancer and a Germline BRCA Mutation. N Engl J Med. 2018 Aug 23; 379(8):753-763.
2. Talazoparib (Talzenna®) Summary of Product characteristics. Last updated 07/12/2021. Accessed July2023. Available at: https://www.ema.europa.eu/en/documents/product-information/talzenna-epar-product-information_en.pdf
3. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V5 2023. Available at: https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/nccp-classification-document-for-systemic-anti-cancer-therapy-sact-induced-nausea-and-vomiting.pdf

Version	Date	Amendment	Approved By
1	01/05/2021		Prof Janice Walshe
2	06/09/2023	Reviewed. Amended dose modification in hepatic impairment as per SPC update. Updated wording for MDS/AML adverse effect as per SPC update. Updated treatment table.	Prof Janice Walshe

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.