Sacituzumab Govitecan Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement status*
As monotherapy for the treatment of adult patients with unresectable or metastatic triple-negative breast cancer (mTNBC) who have received two or more prior systemic therapies, including at least one of them for advanced disease.	C50	00794a	N/A

* This is for post 2012 indications only

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.

Sacituzumab govitecan is administered on day 1 and 8 of a 21 day cycle. Treatment should be continued until disease progression or unacceptable toxicity occurs.

Facilities to treat anaphylaxis MUST be present when the systemic anti-cancer therapy (SACT) is administered.

Day	Drug	Dose	Route	Diluent & Rate	Cycle
1 and 8	Sacituzumab govitecan	10mg/kg	IV infusion Observe for 30 mins post infusion[a]	500ml NaCl 0.9% over 3 hours[b, c, d]	Every 21 days
[a] Patients have to be observed during each infusion and for at least 30 minutes after each infusion for signs or symptoms of infusion-related reactions.					
[b] The initial dose of sacituzumab govitecan should be delivered over three hours as an intravenous infusion. Subsequent infusions: the infusion should be administered over a period of 1 to 2 hours if prior infusions were tolerated.					
[c]The infusion rate of sacituzumab govitecan should be slowed down or infusion interrupted if the patient develops an infusion-related reaction. Treatment should be permanently discontinued if life-threatening infusion-related reactions occur.					
[d] Sacituzumab govitecan should be diluted to a final concentration of 1.1 – 3.4mg/ml.					

ELIGIBILITY:

- Indication as above
- Histologically documented TNBC (absence of HER2, ER, and PR expression)
- ECOG 0-1
- Adequate haematological, renal and liver profile

CAUTION:

- Gilberts disease: If a patient is known to be homozygous for UGT1A1*28, consider starting sacituzumab govitecan at a lower dose. Consider dose escalation depending on toxicity with cycle 1

EXCLUSIONS:

- Hypersensitivity to sacituzumab govitecan or to any of the excipients
- Pregnancy or breastfeeding
- Active uncontrolled infection

PRESCRIPTIVE AUTHORITY:

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

TESTS:

Baseline tests:

- FBC, renal and liver profile
- Blood glucose, electrolytes, magnesium, calcium, phosphate
- ECG if clinically indicated
- Pregnancy test if female of childbearing potential

Regular tests:

- FBC, renal and liver profile prior to each cycle
- Blood glucose, electrolytes, magnesium, calcium, phosphate every second cycle
- ECG if clinically indicated
- Pregnancy test prior to each cycle if female of childbearing potential

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
- Sacituzumab govitecan should not be administered if the absolute neutrophil count (ANC) is < $1.5x10^9$/L on Day 1 of any cycle or if the neutrophil count is <$1.0x10^9$/L on Day 8 of any cycle. Treatment with G-CSF and dose modifications as detailed in table 1 may be required due to severe neutropenia
- The infusion rate of sacituzumab govitecan should be slowed down or infusion interrupted if the patient develops an infusion-related reaction. Sacituzumab govitecan should be permanently discontinued if life-threatening infusion-related reactions occur
- Dose modifications to manage adverse reactions of sacituzumab govitecan are described in Table 1. The sacituzumab govitecan dose should not be re-escalated after a dose reduction for adverse reactions has been made

Management of adverse events:

Table 1: Recommended dose modifications for adverse reactions

Adverse reaction	Occurrence	Dose modification
Severe neutropenia		
Grade 4 neutropenia ≥ 7 days or less if clinically indicated **OR** Grade 3-4 febrile neutropenia **OR** At time of scheduled treatment, Grade 3-4 neutropenia which delays dosing by 2 or 3 weeks for recovery to ≤ Grade 1	First	Administer G-CSF as soon as clinically indicated
	Second	25% dose reduction; administer G-CSF as soon as clinically indicated
	Third	50% dose reduction; administer G-CSF as soon as clinically indicated
	Fourth	Discontinue treatment; administer G-CSF as soon as clinically indicated
At time of scheduled treatment, Grade 3-4 neutropenia which delays dosing beyond 3 weeks for recovery to ≤ Grade 1	First	Discontinue treatment; administer G-CSF as soon as clinically indicated
Severe non-neutropenic toxicity		
Grade 4 non-hematologic toxicity of any duration, **OR** Any Grade 3-4 nausea, vomiting or diarrhoea due to treatment that is not controlled with antiemetics and anti-diarrhoeal agents, **OR** Other Grade 3-4 non-hematologic toxicity persisting > 48 hours despite optimal medical management, **OR** At time of scheduled treatment, Grade 3-4 non-neutropenic hematologic or non-hematologic toxicity, which delays dose by 2 or 3 weeks for recovery to ≤ Grade 1	First	25% dose reduction
	Second	25% dose reduction
	Third	Discontinue treatment
In the event of Grade 3-4 non-neutropenic hematologic or non-hematologic toxicity, Grade 3 nausea or Grade 3-4 vomiting, which does not recover to ≤ Grade 1 within 3 weeks	First	Discontinue treatment

Renal and Hepatic Impairment:

Table 2: Dose modification in renal and hepatic impairment

Renal impairment		Hepatic impairment	
CrCl (ml/min)	**Dose**	**Mild**	No dose adjustment is needed
≥60	No dose adjustment is needed	**Moderate/severe**	No need for dose adjustment is expected
<60	No need for dose adjustment is expected		
Haemodialysis	No need for dose adjustment is expected		

SUPPORTIVE CARE:

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

PREMEDICATIONS:

Pre-infusion treatment, including antipyretics, H1 and H2 blockers, or corticosteroids orally or intravenously is recommended for patients receiving sacituzumab govitecan.

Table 3: Suggested pre-medications prior to sacituzumab govitecan infusion to prevent infusion related reactions

Drug	Dose	Route
Paracetamol	1g	PO 60 minutes prior to infusion
Chlorphenamine	10mg	IV 30 minutes prior to infusion
Famotidine	20mg	IV 30 minutes prior to infusion
Dexamethasone	12mg	PO 30 minutes prior to infusion*
* Dexamethasone dose given to prevent infusion related reactions will also provide anti-emetic cover		

Prophylactic atropine sulphate if required – see adverse effects below.
Atropine should not be used in patients with glaucoma. **(See Adverse Effects/Regimen specific complications below)**

OTHER SUPPORTIVE CARE:

Anti-diarrhoeal therapy **(refer to local policy)**

- As soon as the first liquid stool occurs, the patient should start drinking large volumes of beverages containing electrolytes and an appropriate anti-diarrhoeal therapy must be initiated immediately
- The currently recommended anti-diarrhoeal treatment consists of high doses of loperamide (4 mg for the first intake and then 2 mg every 2 hours)
- This therapy should continue for 12 hours after the last liquid stool and should not be modified
- In no instance should loperamide be administered for more than 48 consecutive hours at these doses, because of the risk of paralytic ileus, nor for less than 12 hours

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS:

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

- **Neutropenia:** Fever or other evidence of infection must be assessed promptly and treated appropriately.
- **Diarrhoea:** Sacituzumab govitecan can cause severe diarrhoea. Treatment should not be administered in case of Grade 3-4 diarrhoea at the time of scheduled treatment and treatment should only be continued when resolved to ≤ Grade 1. At the onset of diarrhoea, and if no infectious cause can be identified, treatment with loperamide should be initiated. Additional supportive measures (e.g. fluid and electrolyte substitution) may also be employed as clinically indicated. Patients who exhibit an excessive cholinergic response to treatment

with sacituzumab govitecan (e.g. abdominal cramping, diarrhoea, salivation, etc.) can receive appropriate treatment (e.g. atropine) for subsequent treatments with sacituzumab govitecan.

- **Hypersensitivity:** Sacituzumab govitecan can cause severe and life-threatening hypersensitivity. Anaphylactic reactions have been observed in clinical trials with sacituzumab govitecan and the use of sacituzumab govitecan is contraindicated in patients with a known hypersensitivity to sacituzumab govitecan. Treatment with sacituzumab govitecan should be permanently discontinued if life-threatening infusion-related reactions occur.
- **Nausea and vomiting:** Sacituzumab govitecan should not be administered in case of Grade 3 nausea or Grade 3-4 vomiting at the time of scheduled treatment administration and treatment should only be continued with additional supportive measures when resolved to ≤ Grade 1. All patients should be given take-home medicinal products with clear instructions for prevention and treatment of nausea and vomiting.
- **Use in patients with reduced UGT1A1 activity (Gilbert's syndrome):** SN-38 (the small molecule moiety of sacituzumab govitecan) is metabolised via uridine diphosphate-glucuronosyl transferase (UGT1A1). Genetic variants of the UGT1A1 gene such as the UGT1A1*28 allele lead to reduced UGT1A1 enzyme activity. Individuals who are homozygous for UGT1A1*28 allele are potentially at increased risk of toxicity following initiation of sacituzumab govitecan treatment. Patients with known reduced UGT1A1 activity should be closely monitored for adverse reactions. When unknown, no testing of UGT1A1 status is required as the management of adverse reactions including the recommended dose modifications will be the same for all patients.
- **Embryo-foetal toxicity:** Based on its mechanism of action, sacituzumab govitecan can cause teratogenicity and/or embryo-foetal lethality when administered to a pregnant woman. Pregnant women and women of childbearing potential should be informed of the potential risk to the foetus. The pregnancy status of females of reproductive potential should be verified prior to the initiation of sacituzumab govitecan.
- **Women of childbearing potential/Contraception in males and females:** Women of childbearing potential have to use effective contraception during treatment and for 6 months after the last dose. Male patients with female partners of childbearing potential have to use effective contraception during treatment with sacituzumab govitecan and for 3 months after the last dose.
- **Sodium:** Sacituzumab govitecan will be further prepared for administration with sodium-containing solution and this should be considered in relation to the total sodium intake to the patient from all sources per day.

DRUG INTERACTIONS:

- Concomitant administration of sacituzumab govitecan with inhibitors of UGT1A1 may increase the incidence of adverse reactions due to potential increase in systemic exposure to SN-38. Sacituzumab govitecan should be used with caution in patients receiving UGT1A1 inhibitors (e.g. propofol, ketoconazole, EGFR tyrosine kinase inhibitors).
- Exposure to SN-38 may be substantially reduced in patients concomitantly receiving UGT1A1 enzyme inducers. Sacituzumab govitecan should be used with caution in patients receiving UGT1A1 inducers (e.g. carbamazepine, phenytoin, rifampicin, ritonavir, tipranavir).
- Current drug interaction databases should be consulted for more information.

REFERENCES:

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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
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Version	Date	Amendment	Approved By
1	23/02/2024		Prof Michaela Higgins

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