

6.06 SACITUZUMAB GOVITECAN, Powder for injection 180 mg, Trodelvy[®], Gilead Sciences Pty Limited

1 Purpose of Submission

- 1.1 The Category 3 submission requested an amendment to the Section 100, Authority Required (STREAMLINED), listing of sacituzumab govitecan (SG) for the treatment of patients with unresectable locally advanced or metastatic triple-negative breast cancer (mTNBC) to request a definition for human epidermal growth factor receptor 2 (HER2) status be added to the clinical criteria of the initial treatment phase restriction.

2 Background

Classification types of breast cancer

- 2.1 Breast cancer can be classified into different types based on the receptors that the tumours express. These types are categorised by the presence or absence of receptors for hormones like oestrogen (ER) and/or progesterone (PR), and also by the expression of the HER2 protein¹.
- 2.2 HER2 expression in breast cancer is measured using Immunohistochemistry (IHC) and In Situ Hybridisation (ISH) with or without a fluorescence (FISH) probe². IHC scoring is a scale from 0 to 3+ as a measure of the level of membrane staining of HER2 protein. ISH/FISH shows if the HER2 gene is amplified (ISH-positive) or not (ISH-negative) by probing chromosome 17 using centromere enumeration probe (CEP) 17. HER2 is considered amplified if the HER2/CEP17 ratio is greater than or equal to 2.0 or if the average HER2 gene copy number is greater than or equal to 4 signals per cell³. Other sources have 6 signals per cell or greater as the amplification threshold. Broadly speaking, HER2 expression is:

¹ National Comprehensive Cancer Network (NCCN) (2024) 'NCCN Guidelines for Patients: Metastatic Breast Cancer', NCCN, pp. 17-22. Available at: https://www.nccn.org/patients/guidelines/content/PDF/stage_iv_breast-patient.pdf (Accessed: 11 February 2025).

² National Comprehensive Cancer Network (NCCN) (2024) 'NCCN Guidelines for Patients: Metastatic Breast Cancer', NCCN, p. 18. Available at: https://www.nccn.org/patients/guidelines/content/PDF/stage_iv_breast-patient.pdf (Accessed: 11 February 2025).

³ Royal College of Pathologists of Australasia (RCPA) (2018) 'ASCO-CAP 2018 HER2 Testing for Breast Cancer Guide', RCPA. Available at: <https://www.rcpa.edu.au/getattachment/fecd094c-aaf4-416b-9ed5-4a61f5ac1a93/ASCO-CAP-2018-HER2-Testing-for-Breast-Cancer-Guide.aspx> (Accessed: 11 February 2025).

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- No expression (HER2-negative): Little to no HER2 protein.
- Low expression (HER2-low): Some HER2 protein but not enough to be HER2-positive.
- High (over) expression (HER2-positive): Strong presence of HER2 protein.

2.3 The 2024 National Comprehensive Cancer Network (NCCN) guidelines have differences in defining HER2 status compared with other prominent guidelines such as the 2018 American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines, the 2023 European Society for Medical Oncology (ESMO) guidelines, and the 2023 American Cancer Society (ACS) guidelines. Table 1 outlines these differences:

Table 1: HER2 status NCCN vs ASCO/CAP

ISH/FISH	IHC 0 (0% staining)	IHC 0 (>0 and <10% staining)	IHC 1+	IHC 2+	IHC 3+
Not amplified (negative)	HER2-negative	ACS HER2-ultralow ASCO/CAP HER2-negative ESMO HER2-ultralow NCCN HER2-negative	ACS HER2-low ASCO/CAP HER2-negative ESMO HER2-low NCCN HER2-negative/low ^a	ACS HER2-low ASCO/CAP HER2-negative/low ESMO HER2-low NCCN HER2-negative/low ^a	HER2-positive
Amplified (positive)	N/A	N/A	ACS HER2-low ASCO/CAP HER2-negative ESMO HER2-low NCCN HER2-positive	HER2-positive	HER2-positive

Source: Compiled by the Secretariat during evaluation using the ACS guidelines⁴, ASCO/CAP guidelines⁵, ESMO⁶, and the NCCN guidelines⁷.

^a In 2022 the NCCN added HER2-low as an additional status⁸.

⁴ American Cancer Society (2025) 'Breast Cancer HER2 Status', American Cancer Society. Available at: <https://www.cancer.org/cancer/types/breast-cancer/understanding-a-breast-cancer-diagnosis/breast-cancer-her2-status.html> (Accessed: 11 February 2025).

⁵ Royal College of Pathologists of Australasia (RCPA) (2018) 'ASCO-CAP 2018 HER2 Testing for Breast Cancer Guide', RCPA. Available at: <https://www.rcpa.edu.au/getattachment/fecd094c-aaf4-416b-9ed5-4a61f5ac1a93/ASCO-CAP-2018-HER2-Testing-for-Breast-Cancer-Guide.aspx> (Accessed: 11 February 2025).

⁶ Annals of Oncology (2023) 'Volume 23 | Supplement 9 | September 2012', Annals of Oncology. Available at: [https://www.annalsofoncology.org/article/S0923-7534\(23\)00693-2/fulltext](https://www.annalsofoncology.org/article/S0923-7534(23)00693-2/fulltext) (Accessed: 11 February 2025).

⁷ National Comprehensive Cancer Network (NCCN) (2024) 'NCCN Guidelines for Patients: Metastatic Breast Cancer', NCCN, p. 18. Available at: https://www.nccn.org/patients/guidelines/content/PDF/stage_iv_breast-patient.pdf (Accessed: 11 February 2025).

⁸ Harris, J. (2022) 'NCCN Adds Trastuzumab Deruxtecan, Sacituzumab Govitecan to Guidelines for HER2-Negative Breast Cancer', OncLive. Available at: <https://www.onclive.com/view/nccn-adds-trastuzumab-deruxtecan-sacituzumab-govitecan-to-guidelines-for-her2-negative-breast-cancer> (Accessed: 11 February 2025).

- 2.4 The ACS and NCCN guidelines define TNBC as a subtype of breast cancer that lacks oestrogen receptors, progesterone receptors, and is HER2-negative^{9,10}. However, the ACS guidelines define this as strictly 0% staining while the NCCN guideline definition includes any staining <10%. The ASCO/CAP and ESMO guidelines include HER2-low within the definition of triple negative^{11,12}.

Registration status

- 2.5 SG is a targeted therapy that was first TGA registered on 6 September 2021. The current TGA product information has SG indicated for the treatment of:
- adult patients with unresectable locally advanced or mTNBC who have received at least two prior systemic therapies, including at least one prior therapy for locally advanced or metastatic disease; and
 - adult patients with unresectable locally advanced or metastatic HR+/HER2- (IHC 0, IHC 1+ or IHC 2+/ISH-) breast cancer who have received endocrine-based therapy (including a CDK4/6 inhibitor) and at least two additional systemic therapies in the locally advanced or metastatic setting.

Current listings

- 2.6 SG is currently listed on the PBS as an Authority Required (STREAMLINED) listing for the treatment of patients with mTNBC.
- 2.7 At its November 2023 meeting, the PBAC had considered trastuzumab deruxtecan (T-DXd) for the treatment of patients with HER2-low (IHC 1+ or IHC 2+ and ISH-negative) unresectable breast cancer and/or metastatic breast cancer. In its consideration it had noted that the HR-/HER2- (IHC 0, IHC 1+, IHC 2+/ISH-) patients eligible to receive SG would also include HR-/HER2-low (IHC 1+ or IHC 2+/ISH-) patients as HER2-low is a subset of patients that would have previously been identified, and treated, as HER2-. The PBAC had not considered T-DXd would replace SG in this population as SG was likely to be used preferentially as the evidence for SG in this population is more robust. The PBAC had considered that as SG is not likely to be

⁹ National Comprehensive Cancer Network (NCCN) (2024) 'NCCN Guidelines for Patients: Metastatic Breast Cancer', NCCN, p. 51. Available at: https://www.nccn.org/patients/guidelines/content/PDF/stage_iv_breast-patient.pdf (Accessed: 11 February 2025).

¹⁰ American Cancer Society (2025) 'Breast Cancer HER2 Status', American Cancer Society. Available at: <https://www.cancer.org/cancer/types/breast-cancer/understanding-a-breast-cancer-diagnosis/breast-cancer-her2-status.html> (Accessed: 11 February 2025).

¹¹ Anders, C.K., Carey, L.A., Hayes, D.F., Burstein, H.J., & Vora, S.R. (2024) 'ER/PR negative, HER2-negative (triple-negative) breast cancer', UpToDate. Available at: <https://www.uptodate.com/contents/er-pr-negative-her2-negative-triple-negative-breast-cancer> (Accessed: 11 February 2025).

¹² Annals of Oncology (2023) 'Volume 23 | Supplement 9 | September 2012', Annals of Oncology. Available at: [https://www.annalsofoncology.org/article/S0923-7534\(23\)00693-2/fulltext](https://www.annalsofoncology.org/article/S0923-7534(23)00693-2/fulltext) (Accessed: 11 February 2025).

replaced by T-DXd, treatment of physician’s choice was an appropriate comparator for the HER2-low population, including the HR- population¹³.

Previous PBAC consideration

- 2.8 At its November 2021 meeting, the PBAC first considered SG for the treatment of mTNBC and did not recommend its listing. It subsequently recommended listing in March 2022 and SG listed on 1 May 2022.
- 2.9 The PBAC considered SG twice thereafter (July and November 2023) for the treatment of adult patients who have HR+/HER2- breast cancer and in both cases were not recommended for PBS listing due to, among other matters, not being considered cost-effective at the price proposed in the submission.
- 2.10 SG has not been previously considered for HR-/HER2-low breast cancer specifically, noting that the submission claimed this population was included in PBS population recommended at the March 2022 PBAC meeting and the PBAC had confirmed this in its November 2023 consideration of T-DXd.

3 Requested listing

- 3.1 The submission requested the following changes to the existing listing with suggested additions in italics and deletions in strikethrough:

MEDICINAL PRODUCT Form	PBS item code	Max. Amount	No.of Rpts
SACITUZUMAB GOVITECAN Injection	12966K (Public) 12944G (Private)	1200 mg	7
Available brands			
Trodelvy (sacituzumab govitecan 180 mg injection, 1 vial)			
Restriction Summary / Treatment of Concept:			
Category / Program: Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals			
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners			
Restriction type: <input checked="" type="checkbox"/> Authority Required – Streamlined			
Caution: This medicine contains a cytotoxic component and causes chemotherapy-like toxicity, in particular, it can cause severe or life-threatening neutropenia and severe diarrhoea. For further information, refer to the Product Information.			
Administrative Advice: No increase in the maximum quantity or number of units may be authorised.			
Administrative Advice: No increase in the maximum number of repeats may be authorised.			
Administrative Advice: Special Pricing Arrangements apply.			

¹³ paragraph 5.1, 5.2, Trastuzumab Deruxtecan, Public Summary Document (PSD), November 2023 PBAC Meeting

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	Episodicity: [Blank]
	Severity: Unresectable locally advanced or metastatic
	Condition: Triple-negative breast cancer
	Indication: Unresectable locally advanced or metastatic triple-negative breast cancer
	Treatment Phase: Initial treatment
	Clinical criteria: Patient must have an HER2 immunohistochemical (IHC) score of 0
	Clinical criteria: The condition must be human epidermal growth factor receptor 2 (HER2) negative
	OR
	Clinical criteria: Patient must be HER2-low defined as a IHC score of 1+ or 2+ and a negative result on in situ hybridization (ISH)
	Clinical criteria: The condition must be human epidermal growth factor receptor 2 (HER2) low
	AND
	Clinical criteria:
	Patient must have progressive disease following two or more prior systemic therapies, at least one of them in the locally advanced or metastatic setting
	AND
	Clinical criteria:
	The condition must be inoperable
	AND
	Clinical criteria:
	Patient must have a World Health Organisation (WHO) Eastern Cooperative Oncology Group (ECOG) performance status score no higher than 1 prior to treatment initiation
	AND
	Clinical criteria:
	The treatment must be the sole PBS-subsidised therapy for this PBS indication
	Prescribing Instructions: HER2-negative is defined as an immunohistochemical (IHC) score of 0
	Prescribing Instruction: HER2-low is defined as an immunohistochemical (IHC) score of 1+ or an IHC score of 2+ and a negative result on in situ hybridization (ISH).

3.2 The additions and deletions to the submission’s requested listing reflect the submission’s intention to remain consistent with what is available in the current T-DXd unresectable and/or metastatic HER2-low breast cancer restrictions.

4 Comparator

4.1 While the submission did not explicitly nominate a comparator, it made frequent references to the T-DXd restriction wording as a comparable example of a drug listed for the treatment of HER2-low metastatic breast cancer that under the traditional nomenclature would have been defined as HER2-negative metastatic breast cancer.

5 Consideration of the evidence

Sponsor hearing

5.1 There was no hearing for this item.

Consumer comments

5.2 The PBAC noted and welcomed the input from Rare Cancers Australia (RCA) and the Medical Oncology Group of Australia (MOGA) via the Consumer Comments facility on the PBS website. While not specific to the request made in this submission, the PBAC noted the RCA consumer comment sought to provide insights into the broader context of breast cancer treatment and patient care. The PBAC also noted that the MOGA expressed its support for the requested change to listing.

Submission claim and evidence

5.3 The submission’s primary claim was that the current restriction wording has the potential to lead to misinterpretation and confusion of a patient’s eligibility for SG. The submission asserted that the potential for a patient to receive less effective treatment and suboptimal clinical care justifies the request to change the restriction wording.

5.4 The submission referenced the ASCENT trial data from the November 2021 PBAC submission and noted that the request to amend existing restrictions aligned with evidence provided in the T-DXd submission for the November 2023 PBAC meeting. The submission claimed the T-DXd submission used data from the ASCENT and DESTINY-Breast04 (DB-04) trials to address the same population. The submission noted that the DB-04 trial used the more recent ESMO classification of HER2 status. Based on the evidence from DB-04, the submission asserted that HER2-low breast cancer emerged as a targetable subset of breast tumours, leading to significant updates to the clinical guidelines for metastatic breast cancer. The 2023 updated ASCO/CAP guidelines consider there is no evidence that IHC 0, IHC 1+ or IHC 2+/ISH- cancers behave differently or have different prognostic and predictive responsiveness for the treatment of HER2- cancers. The ASCO guidelines highlight that it is now best practice to distinguish IHC 0 from 1+ and 2+/ISH- cancers. This updated ASCO/CAP definition of HER2 breast cancer incorporates the contemporary classifications of ISH scored, IHC +/- in relation to HER2 diagnosis. Table 2 shows the submission’s comparison of traditional and contemporary HER2 nomenclature.

Table 2: HER2 nomenclature in contemporary practice.

IHC score	Reflex ISH	HER2 status in clinical practice	
		Traditional/ASCENT	Contemporary/DB-04
0	-	Negative	Negative
1+	-	Negative	Low
2+	Negative	Negative	Low
	Positive	Positive	Positive
3+	-	Positive	Positive

Source: Table 1 of the submission (p5)

This table was based on the ESMO guidelines (HER2-low = IHC 1+ or IHC 2+ and ISH-negative).

5.5 The submission’s request was based on the PBAC accepted contemporary changes of HER2 nomenclature based on the ESMO guidelines (HER2-low (IHC 1+ or IHC 2+ and ISH-negative)) as stated in the T-DXd November 2023 PBAC meeting Public Summary

Document (PSD)¹⁴. In its consideration, PBAC had noted that the HR-/HER2- (IHC 0, IHC 1+, IHC 2+/ISH-) patients eligible to receive SG would also include HR-/HER2-low (IHC 1+ or IHC 2+/ISH-) patients as HER2-low is a subset of patients that would have previously been identified, and treated, as HER2-.

5.6 In the ASCENT trial:

“Clinical sites will use standard ASCO/CAP criteria for the pathological diagnosis of TNBC, defined as negative for estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2). Receptor results will be based on local assessment of the most recent analyzed biopsy (or other pathology specimen). HER2 negative is defined as one of the following: 0 or 1+ by immunohistochemistry (IHC), or if IHC 2+, then fluorescence in situ hybridization (FISH) ratio of HER2 gene: chromosome 17 being less than 2, as per standard guidelines (Wolff 2013). ER- and PR-negative is defined as < 1% of cells expressing hormonal receptors by IHC, as per standard guidelines (Hammond 2010).” (ASCENT Protocol, 2019, p46, provided with the submission to the November 2021 PBAC meeting).

5.7 As a Category 3 submission, no evaluation of the clinical evidence was undertaken.

Economic analysis

5.8 As a Category 3 submission, the economic analysis has not been independently evaluated.

5.9 The submission claimed that amending the restrictions would not change the uptake or cost-effectiveness of the existing arrangements, and therefore did not provide any economic modelling.

Estimated PBS usage and financial implications

5.10 The submission considered that there would be no financial impact noting that there would be no change to the PBS target population and there were no expected increases in the number of patients eligible for treatment.

6 PBAC Outcome

6.1 The PBAC did not recommend an amendment to the listing of sacituzumab govitecan (SG) for the treatment of patients with unresectable locally advanced or mTNBC to include a definition for HER2 status in the clinical criteria of the initial treatment phase restriction.

6.2 The PBAC did not support the submission’s claim that the current restriction wording was likely to be misinterpreted by prescribers when determining patient eligibility for PBS-subsidised treatment with SG. The PBAC advised that the current restriction wording along with the treatment guidelines outlining the line of therapy in this

¹⁴ paragraph 4.6, Trastuzumab Deruxtecan, Public Summary Document (PSD), [November 2023] PBAC Meeting

indication is sufficient for prescribers to exercise clinical discretion to determine patient eligibility and prescribe the most appropriate treatment for their patients.

- 6.3 The PBAC advised that the term 'triple negative' should be retained in the restriction and considered that this term encompasses the intended population previously accepted by the PBAC in its March 2022 consideration.
- 6.4 In relation to the submission's reference to the population of the T-DXd listing and its restriction criteria, the PBAC noted that the mechanism of action of SG does not target HER2 the same way that T-DXd does. The PBAC considered that the restriction wording of the T-DXd listing appropriately encompassed the population it recommended and considered to be cost-effective and that this is not the same population as that which was recommended for SG.
- 6.5 The PBAC noted that this submission is not eligible for an Independent Review as the request is not for an entirely different disease or condition, an objectively different subtype of the same disease(s), or targeting a different population or disease stage.

Outcome:

Not recommended

7 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

8 Sponsor's Comment

Gilead thanks all those who provided consumer comments in support of this request.