Date: 25 October 2021
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Trodelvy

International non-proprietary name: sacituzumab govitecan
Pharmaceutical form: powder for concentrate for solution for infusion
Dosage strength: 180 mg
Route(s) of administration: intravenous use
Marketing Authorisation Holder: Gilead Sciences Switzerland Sàrl
Marketing Authorisation No.: 68179
Decision and Decision date: approved on 09.09.2021

Note:

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

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About Swissmedic

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About the Swiss Public Assessment Report (SwissPAR)

- The SwissPAR is referred to in Article 67 para. 1 of the Therapeutic Products Act and the implementing provisions of Art. 68 para. 1 let. e of the Ordinance of 21 September 2018 on Therapeutic Products (TPO, SR 812.212.21).
- The SwissPAR provides information about the evaluation of a prescription medicine and the considerations that led Swissmedic to approve or not approve a prescription medicine submission. The report focuses on the transparent presentation of the benefit-risk profile of the medicinal product.
- A SwissPAR is produced for all human medicinal products with a new active substance and transplant products for which a decision to approve or reject an authorisation application has been issued.
- A supplementary report will be published for approved or rejected applications for an additional indication for a human medicinal product for which a SwissPAR has been published following the initial authorisation.
- The SwissPAR is written by Swissmedic and is published on the Swissmedic website. Information from the application documentation is not published if publication would disclose commercial or manufacturing secrets.
- The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.
- In addition to the actual SwissPAR, a concise version of SwissPAR that is more comprehensible to lay persons (Public Summary SwissPAR) is also published.

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, Distribution, Metabolism, Elimination
AE	Adverse Event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
AUC0-24h	Area under the plasma concentration-time curve for the 24-hour dosing interval
BC	Breast cancer
BM-neg	patients without known brain metastases at baseline
BRCA	Breast Cancer Gene
Cmax	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DOR	Duration of response
ER	Oestrogen receptor
ERA	Environmental Risk Assessment
GCSF	Granulocyte colony stimulating factor
GLP	Good Laboratory Practice
HER2	Human epidermal growth factor receptor 2
ICH	International Council for Harmonisation
HR	Hazard Ratio
Ig	Immunoglobulin
INN	International Nonproprietary Name
IRC	Independent Review Committee
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
mTNBC	Metastatic triple negative breast cancer
N/A	Not applicable
NO(A)EL	No Observed (Adverse) Effect Level
ORR	Objective response rate
OS	Overall survival
PARP	Poly (ADP-ribose) polymerase
PD	Pharmacodynamics
PD-1	Programmed cell death protein 1
PD-L1	Programmed cell death ligand 1
PFS	Progression-free survival
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PMR	Post-marketing requirement
PopPK	Population PK
PR	Progesterone receptor
PSP	Pediatric Study Plan (US-FDA)
QTc	corrected QT interval
RMP	Risk Management Plan
SAEs	Serious adverse events
SG	Sacituzumab govitecan

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SN-38	Topoisomerase I inhibitor, cytotoxic part of sacituzumab govitecan
SwissPAR	Swiss Public Assessment Report
TEAEs	Treatment emergent adverse events
TNBC	Triple-negative breast cancer

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

New Active Substance status
The applicant requested the status of a new active entity for the active substance sacituzumab govitecan of the medicinal product mentioned above.

2.2 Indication and Dosage

2.2.1 Requested Indication

TRODELVY is indicated for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (mTNBC) who have received at least two prior therapies.

2.2.2 Approved Indication

TRODELVY is indicated for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (mTNBC) who have received at least two prior therapies, at least one of them for metastatic disease (see "Clinical efficacy").

2.2.3 Requested Dosage

The recommended dose of TRODELVY is 10 mg/kg body weight administered as an intravenous infusion once weekly on days 1 and 8 of each 21-day treatment cycle. Continue treatment until disease progression or unacceptable toxicity.
Premedicate with antipyretics and H1 and H2 blockers prior to infusion. Corticosteroids may be used for patients who have had prior infusion reactions.

2.2.4 Approved Dosage

(see appendix)

2.3 Regulatory History (Milestones)

Application	25 January 2021
Formal control completed	26 January 2021
Predecision	25 May 2021
Answers to Predecision	28 June 2021
Labelling corrections	2 August 2021
Answers to Labelling corrections:	13 August 2021
Final Decision	9 September 2021
Decision	approval

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3 Medical Context

In 2020, an estimated 2.26 million female breast cancer (BC) cases were diagnosed worldwide, accounting for nearly 1 in 4 cancer cases among women, and approximately 685,000 women died of the disease. In Switzerland, more than 31,000 women were diagnosed with BC between 2013 and 2017, corresponding to an age-standardised incidence rate of approximately 112 per 100,000, with nearly 7,000 deaths from BC during this period, corresponding to an age-standardised mortality rate of 22.6 per 100,000. Hence, in Switzerland, almost one third of all cancer diagnoses and approximately 18% of all cancer-related deaths in women were due to BC between 2013 and 2017 [All Swiss cancer data extracted from the Swiss national dataset managed by the Foundation National Institute for Cancer Epidemiology and Registration (NICER). Available from http://www.nicer.org/, accessed on 02 February 2021].

Triple-negative breast cancer (TNBC) is defined by the absence of molecular targets such as oestrogen and progesterone receptors or human epidermal growth factor receptor 2 (HER2) overexpression. TNBC is a highly aggressive disease. The recommended first-line treatment for metastatic disease is atezolizumab in combination with nab-paclitaxel if the tumour is programmed death-ligand 1 (PD-L1) positive. For all other patients, chemotherapy is the only treatment available. Overall survival for metastatic TNBC is short (less than 2 years), and there is a clear medical need to improve treatment options for these patients.

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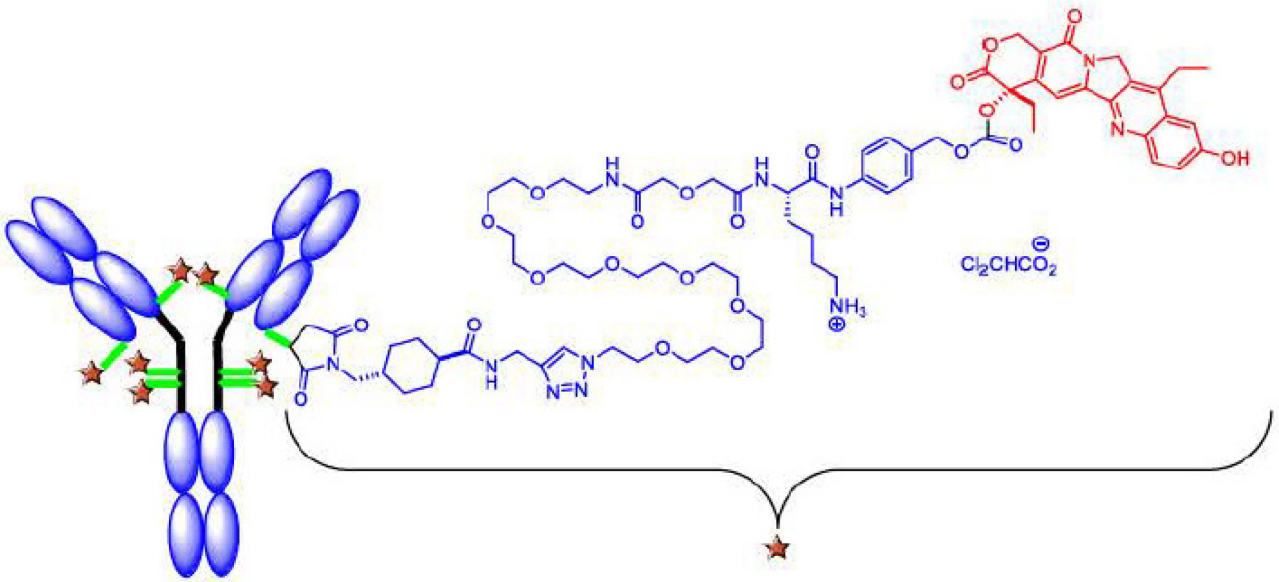
4 Quality Aspects

4.1 Drug Substance

Sacituzumab govitecan is an antibody-drug conjugate made up of SN-38, a topoisomerase I inhibitor that is the active metabolite of irinotecan, coupled by a CL2A linker to the humanised monoclonal antibody hRS7 IgG1κ, which binds to Trop-2 (the trophoblast cell-surface antigen-2). The drug-linker moiety is conjugated to reduced cysteine residues at the sites of the inter-chain disulphide bonds. The average number of drug linkers conjugated to each antibody molecule (drug to antibody ratio, DAR) is 7.0 to 7.5. The chemical structure of sacituzumab govitecan is shown below.



The intermediate drug substance, the antibody hRS7, is produced from a mouse myeloma cell line using a fed-batch production process in a production bioreactor. The other drug substance, intermediate CL2A-SN38, is manufactured by a multiple step chemical synthesis. The sacituzumab govitecan drug substance manufacturing process itself consists of reduction of hRS7, followed by introduction of CL2A-SN38 for conjugation, quenching, removal of impurities by diafiltration, formulation, and bottling.

Several changes were implemented during the development of the drug substance intermediates and drug substance process, including changes to manufacturing site and production scale. However, the analytical comparability studies, which included batch release data, extended characterisation, forced degradation studies, and stability data, demonstrated comparability between the different processes.

The characterisation of the physicochemical and biological properties of the drug substance and its impurities were performed using state-of-the-art methods.

The specifications for drug substance release and stability include relevant tests and acceptance criteria, e.g. for identity, purity and impurities, quantity, and potency. Specifications are based on clinical experience, batch analysis data (release and stability data) and are in conformance with current compendial or regulatory guidelines.

Batch analysis data for non-clinical batches, clinical batches, process performance qualification batches and commercial batches were provided. All specific analytical methods are described and are fully validated.

During storage, no significant changes were observed under the proposed storage conditions.

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4.2 Drug Product

The drug product is a 180 mg single-use sterile, lyophilised powder for concentrate for solution, which is packaged in a Type I clear glass 50 mL vial stoppered with an elastomer stopper and sealed with a 20 mm flip-off overseal. The drug product is formulated with trehalose, polysorbate 80, and 2-(*N*-morpholino) ethane sulfonic acid (MES) hydrate, pH 6.5. The excipients comply with the requirements of the European Pharmacopoeia, with the exception of MES hydrate, pH 6.5. In-house specifications and other relevant information regarding MES hydrate, pH 6.5, are provided.
Prior to use, the drug product is reconstituted with 20 mL of 0.9% (w/v) sodium chloride solution, providing a 10 mg/mL solution. The reconstituted drug product is then diluted in an infusion bag containing 0.9% (w/v) sodium chloride solution for dosing via intravenous infusion.

During process development of drug product, a few changes were implemented, e.g. dosage strength and primary packaging, and a site change was implemented. However, comprehensive characterisation studies, release data, and forced degradation studies, demonstrated comparability between the different processes.

The drug product manufacturing process consists of pooling of formulated drug substance, sterile filtration, filling, lyophilisation, capping, visual inspection, labelling, and secondary packaging.

The drug product manufacturing process was validated with three consecutive process performance qualification batches.

The specifications for drug product release and stability include relevant tests and acceptance criteria, e.g. for identity, purity and impurities, quantity, potency, appearance, pH, osmolality, water content, visible and subvisible particles, bacterial endotoxins, and sterility. The drug product specifications are in conformance with current compendial or regulatory guidelines.

Batch analysis data for several batches, including development batches, clinical batches, process performance qualification batches of both filling lines, and commercial batches were provided. All batch release data comply with the drug product specifications, which were valid at the time of batch release. All specific analytical methods are validated.

The drug product is stored at 2 – 8°C protected from light. A shelf life of 36 months has been accepted.

4.3 Quality Conclusions

The manufacturing processes (drug substance and drug product) are well described and demonstrate a consistent quality of drug substance and drug product. The shelf life of the drug substance and drug product are supported by data from recommended storage conditions, as well as accelerated and stress studies. Safety of the product with regard to viral and non-viral contaminants is adequately addressed.

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5 Nonclinical Aspects

Regarding the marketing authorisation application of TRODELVY (sacituzumab govitecan), the Division Nonclinical Assessment conducted an abridged evaluation, which was based on the FDA assessment report (BLA 761115, dated 17 January 2019) and the supplement to this report, which were provided by the applicant.

Overall, the submitted nonclinical documentation is considered appropriate to support the approval of TRODELVY in the proposed indication. The pharmaco-toxicological profile has been sufficiently characterised. Several safety issues that are of concern for human use were identified in the nonclinical studies. The Nonclinical Safety Specifications in the RMP adequately address these nonclinical findings and their relevance for clinical use. All nonclinical data that are relevant for safety are also adequately mentioned in the information for healthcare professionals.

There is no safety concern regarding excipients and impurities. Potential impurities in drug substance or drug product are adequately controlled. The novel excipient 2-(*N*-morpholino) ethane sulfonic acid hydrate (MES) has been adequately qualified and is considered acceptable from the pharmacology/toxicology perspective.

According to the ERA provided, the risk of sacituzumab govitecan to the environment is assumed to be low.

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6 Clinical and Clinical Pharmacology Aspects

6.1 Clinical Pharmacology

ADME

Absorption

SG (sacituzumab govitecan) is administered by i.v. infusion. Maximum concentrations of SG and free SN-38 (the cytotoxic payload, not covalently bound to the antibody component) were obtained by the end of the infusion.

Distribution

The volume of distribution of SG was 2.96 L.

Metabolism and Excretion

The metabolism of SG has not been studied. The metabolism of the antibody component is assumed to follow usual protein catabolic pathways. SN-38 is eliminated by UGT1A1-dependent glucuronidation, followed by renal and biliary elimination of the SN-38 glucuronide.

The mean half-lives of SG and free SN-38 were 15.3 h and 19.7 h, respectively. The clearance of SG was 0.14 L/hr.

Special Populations / Intrinsic Factors

No clinically significant changes in SG exposure based on body weight, age, race, mild renal impairment, or mild hepatic impairment were identified in a population PK analysis. No dose adjustments are recommended based on these factors.

SG has not been investigated in subjects with moderate or severe hepatic impairment. Since SN-38 is eliminated by UGT1A1-dependent metabolism, hepatic impairment might decrease the elimination of SN-38. Therefore, the use of SG is not recommended in subjects with moderate or severe hepatic impairment. A study to determine a starting dose of SG in subjects with moderate hepatic impairment, will be conducted as a post-marketing requirement (PMR).

SG has not been investigated in subjects with moderate or severe renal impairment. However, since SN-38 is predominantly cleared metabolically and not renally, a limited effect of moderate and severe renal impairment on SN-38 exposure is expected. SG should not be used in subjects with end-stage renal disease.

Genetic variants of UGT1A1 that are associated with reduced enzyme activity, such as the UGT1A1*28 allele, might be associated with a reduced elimination of SN-38. Although the PopPK analysis did not indicate a significant effect of the UGT1A1 genotype on the exposure of free SN-38, such an effect is theoretically plausible, and a subgroup analysis of the safety in patients who were homozygous for the UGT1A1*28 allele indicated an increased safety risk.

Interactions

No dedicated interaction studies have been conducted with SG. However, the elimination of SN-38 is known to be mediated by UGT1A1. In consequence, concomitant use of inhibitors or inducers of UGT1A1 should be avoided.

Pharmacodynamics

Mechanism of Action and Primary Pharmacology

SG is a Trop-2-directed antibody-drug conjugate. Sacituzumab is a humanised antibody that recognises Trop-2. The small molecule, SN-38, is a topoisomerase I inhibitor, which is covalently attached to the antibody by a hydrolysable linker. SG is thought to bind to Trop-2-expressing cancer cells, followed by internalisation and subsequent release of SN-38 via hydrolysis of the linker. SN-38

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interacts with topoisomerase I and prevents re-ligation of topoisomerase I-induced single strand breaks. The resulting DNA damage leads to apoptosis and cell death.

Secondary Pharmacology (Safety)
The effect of SG on cardiac repolarisation was investigated in a PK-QTc substudy of the ASCENT study. There was a positive exposure-response relationship between QTc increases and SN-38 concentrations.

6.2 Dose Finding and Dose Recommendation

Two doses of sacituzumab govitecan (SG), 8 mg/kg and 10 mg/kg, were initially included in the Phase 2 portion of a Phase 1/2 basket study (IMMU-132-01) enrolling patients with solid tumours. Patients were sequentially assigned to the 8 mg/kg dose followed by the 10 mg/kg dose. An interim analysis of Study IMMU-132-01 was performed when 81 and 97 patients with different tumour types had been treated at the two dose levels, respectively. The duration of treatment at the two dose levels was similar, and no important differences in safety were observed between the two dose levels. However, the 10 mg/kg dose compared with the 8 mg/kg dose was associated with a higher objective response rate (ORR), 22% for the 10 mg/kg dose and 10% for the 8 mg/kg dose. The clinical benefit rate was also higher for the 10 mg/kg dose compared to 8 mg/kg [Ocean et al, 2017]. Based on these data, 10 mg/kg SG was selected as the dose for the pivotal study IMMU-132-05 (ASCENT).

6.3 Efficacy

The applicant submitted one pivotal study (IMMU-132-05) and one supportive study (IMMU-132-01) for the requested indication.

Pivotal study IMMU-132-05

IMMU-132-05 is a 1:1 randomised, open-label, phase 3 study comparing sacituzumab govitecan (SG) with treatment of the physician's choice (TPC) in patients with metastatic triple negative breast cancer (mTNBC) having received at least two prior lines of systemic chemotherapy, one of which could have been in the (neo)adjuvant setting, for their disease including a taxane. TPC consisted of single-agent chemotherapy (eribulin, capecitabine, gemcitabine or vinorelbine), all of which are standard treatments in this disease setting. Investigators had to determine the chemotherapy agent before randomisation. Treatment was continued until progression, toxicity, withdrawal of consent or death, whichever occurred first.

The primary endpoint of the study was progression-free survival (PFS) as assessed by an independent review committee (IRC), in patients without known brain metastases at baseline (BM-neg). Secondary endpoints were PFS in the intention-to-treat (ITT) population, overall survival (OS) in the ITT and in the BM-neg population, objective response rate (ORR), duration of response (DOR), quality of life and safety.

Patients were stratified according to prior number of treatment lines (2-3 vs >3), geographic location (North America versus Rest of the World) and presence or absence of known brain metastases at baseline. The number of patients with known and stable brain metastases at baseline was limited to 15%.

It is important to note that approximately 25-27% of mTNBC patients develop brain metastases over the course of their disease [11] and therefore a cap of 15% is not representative of the true incidence of brain metastases in these patients.

The study included women or men with metastatic TNBC, defined as <1% ER and PR and HER2-negative. Measurable disease was required. Patients with brain metastases were allowed if previously treated and stable. Patients had received a minimum of two prior lines of systemic treatment for unresectable locally advanced or metastatic breast cancer (regardless of whether the breast cancer

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was triple negative at that time or not). If patients relapsed within 12 months of (neo)adjuvant treatment, the (neo)adjuvant regimen was counted as one line of prior therapy. PARP-inhibitor therapy in BRCA-mutated patients was considered as a treatment line. Patients must have received a prior taxane unless they were intolerant to it or had a contraindication. Patients also had to present an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, have adequate organ function, no residual toxicities and a life expectancy of 3 months or greater.

Exclusion criteria were numerous. Patients with Gilbert's disease were excluded based on the known risk of toxicity to irinotecan in these patients and the SN-38 payload of SG, which is the active metabolite of irinotecan. Prior malignancies were allowed with at least 3 years of disease-free interval. Active inflammatory bowel disease and history of bowel obstruction were exclusion criteria, as was any history of clinically significant bleeding.

Overall, inclusion and exclusion criteria are reasonable. They certainly lead to a selection bias because patients with heavily pre-treated mTNBC have a very short median OS. However, clinically, only patients in good general condition despite the advanced disease will be offered another line of treatment. Therefore, the patient selection criteria still reasonably reflect the population. However, more than 15% of patients with mTNBC after two or more prior treatment lines will have brain metastases, and these were not adequately represented in this study.

SG was administered on days 1 and 8 of 21-day treatment cycles until progression or toxicity. The single-agent chemotherapy drugs constituting the TPC were administered at registered doses and intervals.

Radiologic assessment was performed every 6 weeks until 36 weeks and every 9 weeks thereafter by computed tomography (CT) or magnetic resonance imaging (MRI). Only patients with known brain metastases at baseline had brain MRIs.

Statistics
A hazard ratio (HR) of 0.667, likely corresponding to a 50% improvement in PFS, was considered to be clinically meaningful in this relapsed/refractory locally advanced or metastatic TNBC patient population. A total of 488 patients were anticipated to be enrolled. The population of patients with brain metastases was limited to 15% (N=74) of the study population. The primary PFS analysis was performed when 425 investigator-defined PFS events had occurred in all randomised patients, provided 315 or more PFS events by IRC review had also occurred in the primary analysis population (i.e., BM-neg population). Assuming that 15% of patients at most had brain metastasis and that there were 13% or fewer PFS events by IRC assessment than by investigator assessment, it was expected that there would be at least 315 PFS events by IRC assessment in the BM-neg population at the time 425 PFS events by investigator assessment were observed in all randomised patients. If the true HR was 0.667 in the IRC review of the BM-neg population, the study had at least 95% power to detect a statistically significant improvement in PFS, with a two-sided type 1 error rate of 5%, if data were analysed after 315 PFS events by IRC assessment. OS was analysed at the time of PFS analysis and also after 330 deaths had occurred in the BM-neg population. The study had approximately 89.5% power to detect an improvement in OS in the BM-neg population, with a two-sided 5% type 1 error rate, assuming that 72% of the planned number of deaths in BM-neg population had occurred at the time of the interim analysis (i.e., 238 deaths) and the true HR for OS was 0.7.

The overall type I error rate was controlled by a hierarchical testing strategy. The primary endpoint of PFS by IRC assessment was analysed and tested first in the BM-neg population. If the primary analysis test was significant, subsequent key secondary endpoints (OS in the BM-neg population, PFS by IRC assessment in the ITT population, OS in the ITT population) were tested in a sequential manner, where a given hypothesis was only declared statistically significant if all hypotheses above it in the hierarchy were also statistically significant.

The protocol was amended six times. The most important amendments were an increase in sample size from 328 to 488 and, in Amendment 5, the removal of the interim futility analysis.

Assumptions for PFS and OS are reasonable, and the statistical analysis plan is adequate.

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Results: Study Population

The study screened 730 patients, and 529 patients were randomised, 267 to SG and 262 to TPC. Most patients did not have brain metastases at baseline, and only 61 patients with known brain metastases were randomised. In total, 32 patients were randomised to SG and 29 to TPC. In the control arm, 38 (14.5%) patients were randomised but did not receive treatment.

At the time of study completion (11 March 2020), 15 patients (6.4%) were still on study treatment in the SG arm versus none in the control arm. The most common reasons for study discontinuation in the control arm were death (76%) and withdrawal of consent (10%). These were also the main reasons for study discontinuation in the SG arm, but to a lesser extent (64% death, 3% withdrawal of consent).

Baseline demographic and disease characteristics were balanced between the two arms. Only two male patients were enrolled in the study and they were both randomised to the SG arm. Nearly all patients (95%) had prior breast cancer surgery. Approximately 27% had received prior PD-1/PD-L1 therapy and 80% had prior (non-brain) radiotherapy.

Overall, patients in the SG arm received concomitant medication more frequently compared to patients in the control arm. Some of these medications reflect the use of corticosteroids and anti-histamines to prevent infusion reactions. However, there was also more use of anti-emetics, likely reflecting the emetogenic potential of SG. Nearly half of the patients in the SG arm (46.4%) received granulocyte colony stimulating factors (GCSF) compared to just under 20% of patients in the control arm. Patients in the SG arm also received more antibacterial and antiviral medication. Overall, there was an important imbalance between the two treatment arms, with a large number of medications being administered more frequently in the SG arm.

Results: Efficacy

The IRC-assessed median PFS in the brain metastases-negative (BM-neg) population is 5.6 months (95% CI: 4.3, 6.3) in the SG arm versus 1.7 months (95% CI: 1.5, 2.6) in the control arm. This observed benefit of 3.9 months PFS with an HR of 0.41 (95% CI: 0.32, 0.52) is statistically significant ($p < 0.0001$) and clinically meaningful in this heavily pre-treated patient population. No PFS benefit is observed in the small group of patients with brain metastases. Median PFS is 2.8 months (95% CI: 1.5, 3.9) in the SG arm versus 1.6 months (95% CI: 1.3, 2.9) in the control arm. All sensitivity analyses performed for PFS are consistent with the primary analysis. All subgroups independent of age, race, number of prior therapies, and region of the world, Trop-2 expression, and presence or absence of liver metastases show a benefit for SG over control.

The secondary endpoint of PFS in the ITT population also shows a statistically significant PFS benefit of SG over TPC, with 4.8 months median PFS versus 1.7 months, respectively. The HR is 0.43 (95% CI 0.35, 0.54) with a p-value of <0.0001. However, this finding is expected given the 15% enrolment cap on brain metastases-positive patients. Therefore, the additional patients in the ITT population are unlikely to change the finding of the majority of patients without brain metastases.

The secondary endpoint of OS in BM-neg patients was also reached. Median OS is 12.1 months (95% CI: 10.7, 14.0) in the SG arm versus 6.7 months (95% CI: 5.8, 7.7) in the control arm. The HR is 0.48 (95% CI: 0.38, 0.59) and the p-value <0.0001. In the ITT population, median OS is 11.8 months in the SG arm and 6.9 months in the control arm. As for PFS, no benefit was observed in the small brain metastases-positive population, with a median OS of 6.8 months (95% CI: 4.7, 14.1) in the SG arm versus 7.5 months (95% CI: 4.7, 11.1) in the control arm. The HR is 0.87 (95% CI: 0.47, 1.63).

Other secondary endpoints were objective response rate (ORR) and duration of response (DOR). SG was superior to TPC in these secondary endpoints.

Supportive study IMMU-132-001

The supportive study IMMU-132-01 was a phase 1/2 dose-finding and dose-expansion study. It included 144 patients with TNBC, of whom 108 had received at least two prior lines of treatment for

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metastatic disease. The recommended phase 2 dose was 10 mg/kg on days 1 and 8 of 21-day cycles.

Results from this study show an ORR of 33%, a clinical benefit rate (CBR) of 45%, a median PFS of 5.6 months and a median OS of 13.0 months. While this is an uncontrolled study, the results are consistent with those observed in the randomised phase 3 study and are considered supportive.

6.4 Safety

The summary of clinical safety provides data on 660 patients in total. There are three safety pools. The IMMU-132-05 safety pool comprises 258 patients treated with SG and 224 patients treated with active control (TPC; eribulin, gemcitabine, capecitabine, vinorelbine). The TNBC safety pool (366 patients) comprises the patients from study IMMU-132-05 and IMMU-132-01 with TNBC and two prior lines of treatment. The IMMU-132-01 study had enrolled 144 patients with TNBC, however, those patients who had not received two prior lines of treatment in the metastatic setting were not included in the TNBC pool but in the all-treated SG safety pool (660 patients).

Exposure
Treatment duration was similar between the randomised phase 3 study IMMU-132-05 (4.4 months) and all SG treated patients (4.1 months), and longer than for control patients (1.3 months). Dose reductions were observed in approximately 30% of all SG safety pools, and most patients had only one dose reduction. Mean dose intensity was >90%, and the median dose intensity was >98% for all safety pools (IMMU-132-05, TNBC, and all). Most patients discontinued treatment due to progressive disease (PD), 84% in the TNBC safety pool and 75% in the all-treated safety pool. However, in the control arm of the phase 3 IMMU-132-05 study, 8% of patients discontinued due to withdrawal of consent. Only 3.8% of patients discontinued SG for adverse events (AEs) in the TNBC pool and 6.8% in the all-treated safety pool.

In study IMMU-132-05, AEs leading to treatment interruptions were more frequent in the SG arm (63%) compared to the control arm (39%). Most frequent reasons for treatment interruption were haematological toxicity (despite higher use of GCSF in the SG arm compared to the control arm), infectious complications and gastrointestinal toxicity (diarrhoea, nausea, vomiting). These frequencies were similar in all safety pools.

Incidence of AEs
Treatment emergent adverse events (TEAEs) (98% vs 86%), TEAEs of ≥ grade 3 (75% vs 65%), and TEAEs leading to study drug interruption (55% vs 39%) were more frequent in the SG safety pools compared to the control arm of the IMMU-132-05 study (TPC). Serious TEAEs were similar in incidence in the two TNBC safety pools (~27%) and comparable with the incidence in the control arm (28%) of the phase 3 study for TNBC. However, in the all-SG treated safety pool, the incidence of serious AEs (SAEs) was higher (35%).

Most frequent AEs
The most frequent AEs were gastrointestinal toxicity, haematological toxicity and general conditions. The preferred terms were **diarrhoea** (64%), **nausea** (67%), **vomiting** (40%), **constipation** (38%), **abdominal pain** (22%), **neutropenia** (61%), **anaemia** (41%), **fatigue** (52%), **headache** (17%), **alopecia** (44%), and **rash** (21%). The frequencies of these AEs were comparable between the three safety pools. All of these AEs were considered treatment-related.

Grade 3/4 AEs
There were only a few grade 4 AEs and mostly involved neutropenia. In the IMMU-132-05 study, there was one grade 4 nausea and 1 grade 4 vomiting AE. Grade 3 diarrhoea was observed in 11% of patients in the IMMU-132-05 study, grade 3 neutropenia (including neutrophil count decreased) in 28%, grade 3 anaemia in 9% and grade 3 nausea and abdominal pain in 3% of patients in each case.

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Deaths
In the all-patient safety pool, there were 12 on-treatment deaths. There was one death considered treatment-related in the all-treated SG safety pool, but none in the TNBC safety pool. The one death considered treatment-related in the all-treated safety pool was due to an aspiration pneumonia in a patient with NSCLC who had presented nausea after each administration of SG.

Serious AEs
In the IMMU-132-05 study, the overall incidence of SAEs was similar between the two treatment arms. In the SG arm, more patients had **febrile neutropenia** (5%), **diarrhoea** (3.5%) and **pneumonia** (2.7%). Here too, the numbers were comparable among the three safety pools.

Special populations
Patients homozygous for the UGT1A1 *28 allele show increased toxicity for diarrhoea, neutropenia and anaemia compared to patients with a *1 homozygous or heterozygous genotype.

6.5 Final Clinical and Clinical Pharmacology Benefit Risk Assessment

Triple negative breast cancer (TNBC) is a highly aggressive disease defined by the absence of molecular targets such as hormone receptors or HER2 overexpression. Recommended first-line treatment for metastatic disease is atezolizumab in combination with nab-paclitaxel if the tumour is PD-L1 positive. For all other patients, chemotherapy is the only treatment available. Overall survival for metastatic TNBC is short, and there is a clear medical need to improve treatment options for these patients.

The PK characteristics of sacituzumab govitecan and of free SN-38 have been investigated sufficiently. No dose adjustments are required based on age, ethnicity or due to mild renal or hepatic impairment. SG has a limited potential for drug-drug interactions (only with UGT1A1 inhibitors and inducers).

The randomised IMMU-132-05 study compared sacituzumab govitecan (SG) with treatment of physician's choice (TPC), which consisted of single-agent chemotherapy with eribulin, gemcitabine, capecitabine or vinorelbine. The primary endpoint of progression-free survival in patients without known brain metastases at baseline was reached, with an improvement of 3.9 months, from 1.7 to 5.6 months median PFS. The hazard ratio is 0.41 and the result is highly statistically significant and clinically meaningful. In addition, OS was also significantly improved from 6.7 to 12.1 months in the brain metastases-negative patient population. This 5.4 month benefit in OS is statistically significant and clinically meaningful.

Patients with brain metastases were only allowed to enrol if they had stable lesions, and a maximum of 15% of patients with brain metastases were allowed. The study enrolled 61 patients with brain metastases of whom 29 were randomised to the control arm and 32 to the SG arm. There was no apparent benefit of SG over control in PFS or OS in this small population. This finding is adequately reflected in the information for healthcare professionals.

Although SG is an antibody-drug conjugate, the toxicity profile is linked to the drug moiety of SN-38, with diarrhoea, nausea, vomiting and abdominal pain, haematological toxicity with neutropenia and anaemia as well as fatigue. Electrolyte imbalances are also observed, likely due - at least in part - to diarrhoea. Alopecia is observed in nearly half of all patients and is mostly of grade 2 (complete hair loss). Nevertheless, there is no excess of fatal AEs, and the toxicity seems to be manageable with supportive treatment such as anti-diarrhoeal medication, anti-emetic treatment and hematologic growth factors.

The PK of SG has not been assessed in subjects with moderate or severe hepatic or renal impairment. The risk arising from this lack of data is considered to be low in the case of renal

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impairment and could be addressed by appropriate wording in the information for healthcare professionals.
In case of hepatic impairment, since there is a relevant risk that the exposure of SN-38 might be elevated, the use of SG in patents with moderate and severe hepatic impairment is not recommended. A study to determine a starting dose of SG in subjects with moderate hepatic impairment, will be conducted as a PMR.

The immunogenicity of SG has not yet been characterised, because no validated assays with sufficient drug tolerance and sensitivity have been developed so far. Analyses to characterise the immunogenicity of SG will be conducted as a PMR.

Patients with metastatic triple negative breast cancer have an abysmal prognosis and limited treatment options. SG has demonstrated efficacy in prolonging not only progression-free survival but also overall survival in these heavily pre-treated patients. The OS benefit of 4.9 months in the ITT population is clinically meaningful. The toxicity is high but seems manageable with supportive treatment, as in other oncologic diseases. Therefore, the risk-benefit is considered positive. While patients with brain metastases did not have a demonstrated benefit, they did not seem to suffer a detriment and they have an important medical need. This issue of a potential lack of benefit in patients with brain metastases is adequately reflected in the information for healthcare professionals. In addition, the FDA has asked for a post-marketing commitment of the sponsor to provide further data in patients with brain metastases treated with SG.

6.6 Approved Indication and Dosage

See information for healthcare professionals in the Appendix.

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7 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order to further investigate and monitor the risks as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisations.

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8 Appendix

8.1 Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to Trodelvy was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the reference document, which is valid and relevant for the effective and safe use of medicinal products in Switzerland, is the information for healthcare professionals approved and authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. The Authorisation Holder is responsible for the correct translation of the text. Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

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▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the “Undesirable effects” section for advice on the reporting of adverse reactions.

TRODELVY®

Composition

Active substances

Sacituzumab govitecan.
Manufactured from genetically modified murine myeloma cells.

Excipients

2-(N-morpholino) ethane sulfonic acid (MES), polysorbate 80 (E433) and trehalose dihydrate.

Pharmaceutical form and active substance quantity per unit

Powder for concentrate for solution for infusion.

Each single-dose vial contains 180 mg sacituzumab govitecan as lyophilized, off-white to yellowish powder for reconstitution.

Reconstitution with 20 mL of 0.9% sodium chloride solution results in a concentration of 10 mg/mL with a pH of 6.5.

Indications/Uses

TRODELVY is indicated for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (mTNBC) who have received at least two prior therapies, at least one of them for metastatic disease (see “Clinical efficacy”).

Dosage/Administration

The recommended dose of TRODELVY is 10 mg/kg administered as an intravenous infusion once weekly on Days 1 and 8 of 21-day treatment cycles. Continue treatment until disease progression or unacceptable toxicity. Do not administer TRODELVY at doses greater than 10 mg/kg.

Administer TRODELVY as an intravenous infusion only. Do not administer as an intravenous push or bolus.

First infusion: Administer infusion over 3 hours. Observe patients during the infusion and for at least 30 minutes following the initial dose, for signs or symptoms of infusion-related reactions (see “Warning and Precautions”).

Subsequent infusions: Administer infusion over 1 to 2 hours if prior infusions were tolerated. Observe patients during the infusion and for at least 30 minutes after infusion.

To ensure traceability of biotechnological medicinal products, it is recommended that the trade name and batch number should be documented for each treatment.

Premedication

Prior to each dose of TRODELVY, premedication for prevention of infusion reactions and prevention of chemotherapy-induced nausea and vomiting (CINV) is recommended.

- Premedicate with antipyretics and H1 and H2 blockers prior to infusion. Corticosteroids may be used for patients who had prior infusion reactions.
- Premedicate with a two or three drug combination regimen (e.g., dexamethasone with either a 5-HT3 receptor antagonist or an NK1 receptor antagonist, as well as other drugs as indicated).

Dose adjustment following undesirable effects/interactions

Infusion-related Reactions

Reduce the infusion rate by half or interrupt the infusion of TRODELVY, if the patient develops an infusion-related reaction. Permanently discontinue TRODELVY for life-threatening infusion-related reactions (see “Warnings and Precautions”).

Dose Modifications for Adverse Reactions

Withhold or discontinue TRODELVY to manage adverse reactions as described in Table 1. Do not re-escalate the TRODELVY dose after a dose reduction for adverse reactions has been made.

Table 1: Dose Modifications for Adverse Reactions

Adverse Reaction	**Occurrence**	**Dose Modification**
Severe Neutropenia (see “Warnings and Precautions”)		
Grade 4 neutropenia ≥ 7 days, OR Grade 3 febrile neutropenia (absolute neutrophil count < 1000/mm^3 and fever ≥ 38.5°C), 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 granulocyte-colony stimulating factor (G-CSF)
	Second	25% dose reduction
	Third	50% dose reduction
	Fourth	Discontinue treatment
At time of scheduled treatment, Grade 3-4 neutropenia which delays dosing beyond 3 weeks for recovery to ≤ Grade 1	First	Discontinue treatment
Severe Non-Neutropenic Toxicity		
Grade 4 non-hematologic toxicity of any duration,	First	25% dose reduction

Adverse Reaction	Occurrence	Dose Modification
OR Any Grade 3-4 nausea, vomiting or diarrhea due to treatment that is not controlled with antiemetics and anti-diarrheal agents (see “Warnings and Precautions”), 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	Second	50% dose reduction
	Third	Discontinue treatment
In the event of Grade 3-4 non-neutropenic hematologic or non-hematologic toxicity, which does not recover to ≤ Grade 1 within 3 weeks	First	Discontinue treatment

Patients with hepatic impairment

No adjustment to the starting dose is required when administering TRODELVY to patients with mild hepatic impairment (bilirubin ≤1.5 x ULN and AST/ALT <3 x ULN).

The exposure of TRODELVY in patients with mild hepatic impairment (bilirubin ≤ ULN and AST > ULN, or bilirubin > 1.0 to 1.5 x ULN and AST of any level; n=59) was similar to patients with normal hepatic function (bilirubin or AST < ULN; n=191).

The safety of TRODELVY in patients with moderate or severe hepatic impairment has not been established. TRODELVY has not been studied in patients with serum bilirubin > 1.5 x ULN, or AST and ALT > 3 x ULN in patients without liver metastases, or AST and ALT > 5 x ULN with liver metastases. The use of TRODELVY is not recommended in these patients.

Patients with renal impairment

No adjustment to the starting dose is required when administering TRODELVY to patients with mild renal impairment. TRODELVY has not been studied in patients with moderate or severe renal impairment, or end-stage renal disease (see “Pharmacokinetics”). The use of TRODELVY is not recommended in patients with end-stage renal disease (CrCl ≤ 15 mL/min).

Children and adolescents

The safety and efficacy of TRODELVY in children and adolescents have not been demonstrated.

Mode of administration

- Administer TRODELVY as an intravenous infusion. Protect infusion bag from light.
- An infusion pump may be used.
- Do not mix TRODELVY, or administer as an infusion, with other medicinal products.
- Upon completion of the infusion, flush the intravenous line with 20 mL 0.9% sodium chloride solution.
- Detailed instructions for handling of TRODELVY are provided in “Other information”.

Contraindications

TRODELVY is contraindicated in patients who have experienced a severe hypersensitivity reaction to TRODELVY, with chronic inflammatory bowel disease and/or bowel obstruction, with bilirubin levels > 3 ULN, or on dialysis (see “Warnings and Precautions”).

Warnings and precautions

Neutropenia

TRODELVY can cause severe or life-threatening neutropenia that may result in death. Neutropenia occurred in 62% of patients treated with TRODELVY, leading to permanent discontinuation of TRODELVY in 0.5% of patients. Grade 3-4 neutropenia occurred in 47% of patients. Febrile neutropenia occurred in 6% of patients.

Withhold TRODELVY for absolute neutrophil count below 1500/mm^3 on Day 1 of any cycle or neutrophil count below 1000/mm^3 on Day 8 of any cycle. Withhold TRODELVY for neutropenic fever. Dose modifications may be required due to neutropenia (see “Dosage/Administration”).

Diarrhea

TRODELVY can cause severe diarrhea. Withhold TRODELVY for Grade 3-4 diarrhea at the time of scheduled treatment administration and resume when resolved to ≤ Grade 1 (see “Dosage/Administration”).

At the onset of diarrhea, evaluate for infectious causes and if negative, promptly initiate loperamide, 4 mg initially followed by 2 mg with every episode of diarrhea for a maximum of 16 mg daily. Discontinue loperamide 12 hours after diarrhea resolves. 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 TRODELVY (e.g., abdominal cramping, diarrhea, salivation, etc.) can receive appropriate premedication (e.g., atropine) for subsequent treatments.

Hypersensitivity and Infusion-Related Reactions

TRODELVY can cause severe and life-threatening hypersensitivity. Anaphylactic reactions have been observed in clinical trials with TRODELVY (see “Contraindications”).

Hypersensitivity reactions within 24 hours of dosing occurred in 37% of patients treated with TRODELVY. Grade 3-4 hypersensitivity occurred in 2% of patients treated with TRODELVY. The incidence of hypersensitivity reactions leading to permanent discontinuation of TRODELVY was 0.3%.

Pre-infusion medication for patients receiving TRODELVY is recommended. Observe patients closely for infusion-related reactions during each TRODELVY infusion and for at least 30 minutes after completion of each infusion (see “Dosage/Administration”). Medication to treat such reactions, as well as emergency equipment, should be available for immediate use.

Nausea and Vomiting

TRODELVY is emetogenic. Premedicate with a two or three drug combination regimen (e.g., dexamethasone with either a 5-HT3 receptor antagonist or an NK-1 receptor antagonist as well as other drugs as indicated) for prevention of chemotherapy-induced nausea and vomiting (CINV).

Withhold TRODELVY doses for Grade 3 nausea or Grade 3-4 vomiting at the time of scheduled treatment administration and resume with additional supportive measures when resolved to ≤ Grade 1 (see “Dosage/Administration”).

Additional antiemetics and other supportive measures may also be employed as clinically indicated. All patients should be given take-home medications with clear instructions for prevention and treatment of nausea and vomiting.

Use in Patients with Reduced UGT1A1 Activity

Individuals who are homozygous for the uridine diphosphate-glucuronosyl transferase 1A1 (UGT1A1)*28 allele are at increased risk for neutropenia, febrile neutropenia, and anemia and may be at increased risk for other adverse reactions following initiation of TRODELVY treatment.

Closely monitor patients with known reduced UGT1A1 activity for adverse reactions (see “Dosage/Administration”).

Embryo-Fetal Toxicity

Based on its mechanism of action, TRODELVY can cause teratogenicity and/or embryo-fetal lethality when administered to a pregnant woman. TRODELVY contains a genotoxic component, SN-38, and targets rapidly dividing cells (see “Properties/Effects”, “Pregnancy, lactation”, and “Preclinical data”).

Interactions

Effect of other medicinal products on TRODELVY

UGT1A1 Inhibitors

Concomitant administration of TRODELVY with inhibitors of UGT1A1 may increase the incidence of adverse reactions due to potential increase in systemic exposure to SN-38 (see “Warnings and Precautions” and “Properties/Effects”). The administration of UGT1A1 inhibitors with TRODELVY should be avoided.

UGT1A1 Inducers

Exposure to SN-38 may be substantially reduced in patients concomitantly receiving UGT1A1 enzyme inducers (see “Warnings and Precautions” and “Properties/Effects”). The administration of UGT1A1 inducers with TRODELVY should be avoided.

Pregnancy, lactation

Women of childbearing potential or their partners

Verify the pregnancy status of females of reproductive potential prior to the initiation of TRODELVY. Advise females of reproductive potential to use effective contraception during treatment with TRODELVY and for 6 months after the last dose.

Because of the potential for genotoxicity, advise male patients with female partners of reproductive potential to use effective contraception during treatment with TRODELVY and for 3 months after the last dose.

Pregnancy

Based on its mechanism of action, TRODELVY can cause teratogenicity and/or embryo-fetal lethality when administered to a pregnant woman. There are no available data in pregnant women to inform the drug-associated risk. TRODELVY contains a genotoxic component, SN-38. Irinotecan and its active metabolite SN-38 are toxic to rapidly dividing cells and have been shown to be teratogenic in animal studies (see “Properties/Effects” and “Preclinical data”). Advise pregnant women and females of reproductive potential of the potential risk to a fetus

Lactation

There is no information regarding the presence of sacituzumab govitecan in human milk. Irinotecan and its active metabolite SN-38 are excreted in human milk, as has also been shown in animal studies. The effects on the breastfed child or the effects on milk production are not known. Because of

the potential for serious adverse reactions in a breastfed child, advise women not to breastfeed during treatment and for 1 month after the last dose of TRODELVY.

Fertility

Females/Males

Based on findings in animals, TRODELVY may impair fertility in males and females of reproductive potential (see “Preclinical data”).

Effects on ability to drive and use machines

No corresponding studies have been performed. However, since TRODELVY may cause nausea and dizziness, caution is recommended when driving a vehicle or using machines (see “Undesirable effects”).

Undesirable effects

Summary of the safety profile

The most common (≥ 3%) dose-limiting adverse reaction reported in patients receiving TRODELVY was neutropenia. The most common (≥ 3%) serious adverse reactions were febrile neutropenia, diarrhea, and pneumonia.

List of adverse reactions

The adverse reactions were calculated from pooled data from two clinical studies involving 660 patients who received TRODELVY 10 mg/kg, including 366 patients with TNBC. The adverse reactions are arranged according to MedDRA system organ classes and sorted by frequencies estimated from all reported events, using the conventional frequencies as follows: very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000).

Infections and infestations

Very common: urinary tract infection (13.8%), upper respiratory tract infection (12.7%).
Common: bronchitis, pneumonia.

Blood and lymphatic system disorders
Very common: neutropenia (60.8%), anaemia (41.2%), leukopenia (18.0%).
Common: lymphopenia, febrile neutropenia.

Immune system disorders
Very common: Hypersensitivity (36.8%).

Metabolism and nutrition disorders

Very common: decreased appetite (32.3%), hypokalaemia (16.7%), hypomagnesaemia (15.3%), dehydration (12.3%), hypophosphatemia (11.7%), hyperglycaemia (10.0%).
Common: hypocalcaemia.

Psychiatric disorders
Very common: insomnia (11.2%).

Nervous system disorders
Very common: headache (17.1%), dizziness (13.8%).
Common: dysgeusia.

Respiratory, thoracic and mediastinal disorders
Very common: cough (22.3%), dyspnoea (19.7%).
Common: epistaxis.

Gastrointestinal disorders
Very common: nausea (66.7%), diarrhea (63.5%), vomiting (39.8%), constipation (37.9%), abdominal pain (21.8%).
Common: stomatitis, abdominal distension.

Skin and subcutaneous tissue disorders
Very common: alopecia (43.6%), rash (23.8%), pruritus (11.4%).
Common: dry skin.

Musculoskeletal and connective tissue disorders
Very common: back pain (16.8%), arthralgia (12.1%).

General disorders and administrative site conditions
Very common: fatigue (53.8%), oedema peripheral (12.7%).

Investigations
Very Common: weight decreased (13.2%).

Description of specific adverse reactions and additional information

Neutropenia

Febrile neutropenia occurred in 5.8% (38/660) of patients treated with TRODELVY. One patient (< 1%) had febrile neutropenia leading to permanent discontinuation.
The incidence of Grade 1-4 neutropenia was 60.8% (401/660). Grade 4 neutropenia occurred in 14.8%. Two of 660 patients (< 1%) patients permanently discontinued treatment due to neutropenia.

The median time to onset of neutropenia following the start of the first treatment cycle was 17 days. Neutropenia was reversible with a median duration of 8 days.

Use in patients with reduced UGT1A1 activity

In 88.8% (586/660) of patients with TNBC or other solid tumours who received TRODELVY (up to 10 mg/kg on Days 1 and 8 of a 21-day cycle) and had retrospective UGT1A1 genotype results available, the incidence of Grade 4 neutropenia was 27% (19/70) in patients homozygous for the UGT1A1*28 allele, 15% (37/246) in patients heterozygous for the UGT1A1*28 allele and 13% (33/261) in patients homozygous for the wild-type allele.

Diarrhea

Diarrhea occurred in 63.5% (419/660) of patients. Events of Grade 3 occurred in 10.3% (68/660) of patients. No Grade 4 events were reported. Five of 660 patients (< 1%) discontinued treatment because of diarrhea. Neutropenic colitis was observed in < 1% (3/660) of patients.
The median time to onset of diarrhea following the start of the first treatment cycle was 13 days. The median duration of diarrhea was 8 days.

Hypersensitivity

Hypersensitivity reactions within 24 hours of dosing occurred in 36.8% (243/660) of patients treated with TRODELVY. Grade 3-4 hypersensitivity occurred in 1.5% (10/660) of patients treated with TRODELVY. The incidence of hypersensitivity reactions leading to permanent discontinuation of TRODELVY was 0.3% (2/660).

Nausea and vomiting

Nausea occurred in 66.7% (440/660) of patients. Grade 3 and Grade 4 nausea occurred in 4.4% (29/660) of patients.
Vomiting occurred in 39.8% (263/660) of patients. Grade 3 and Grade 4 vomiting occurred in 2.9% (19/660) of these patients.

Immunogenicity

The immunogenicity of TRODELVY has not yet been fully characterized. The incidence of anti-drug antibodies (ADAs) depends to a large extent on the sensitivity and specificity of the test. Furthermore, the observed incidence of antibody positivity (including neutralizing antibodies) may be influenced by multiple factors in one test, such as the testing method, sample handling, the time the sample was taken, concomitant medications, and the underlying disease. Therefore, a comparison of the incidence of anti-TRODELVY antibodies with the incidence of antibodies to other medications may be misleading.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

There is no information on overdose with TRODELVY. In a clinical trial, planned doses of up to 18 mg/kg (approximately 1.8 times the maximum recommended dose of 10 mg/kg) of TRODELVY were administered. In these patients, a higher incidence of severe neutropenia was observed.

In case of overdose, patients should be closely monitored for signs or symptoms of adverse reactions, in particular severe neutropenia, and appropriate treatment instituted.

Properties/Effects

ATC code

Not yet assigned.

Mechanism of action

Sacituzumab govitecan is a Trop-2-directed antibody-cytotoxic agent SN-38 conjugate. Sacituzumab is a humanized antibody that recognizes Trop-2. The small molecule, SN-38, is a topoisomerase I inhibitor, which is covalently attached to the antibody by a linker. Pharmacology data suggest that sacituzumab govitecan binds to Trop-2-expressing cancer cells and is internalized with the subsequent release of SN-38 via hydrolysis of the linker. SN-38 interacts with topoisomerase I and prevents re-ligation of topoisomerase I-induced single strand breaks. The resulting DNA damage leads to apoptosis and cell death. Sacituzumab govitecan decreased tumor growth in mouse xenograft models of triple-negative breast cancer.

Pharmacodynamics

Cardiac electrophysiology

The effect of TRODELVY on the QTc interval has been assessed in a dedicated pharmacokinetic QTc-substudy (n=17, evaluable patients) of the phase 3 ASCENT-study. This found a positive link between exposure to SN-38 and the QTc interval prolongation. At the recommended dose, the maximum mean change from baseline was 9.7 msec (the upper limit of the two-sided 90% confidence interval was 16.8 msec).

Clinical efficacy

The effectiveness of TRODELVY in the treatment for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (mTNBC) who have received at least two prior therapies was investigated in two studies: ASCENT (IMMU-132-05) and IMMU-132-01.

ASCENT (IMMU-132-05)

ASCENT was an international Phase 3, multicenter, open-label, randomized study conducted in 529 patients with unresectable locally advanced or metastatic triple-negative breast cancer (mTNBC) who had relapsed after at least two prior chemotherapies (no upper limit) for breast cancer. All patients received previous taxane treatment in either the adjuvant, neoadjuvant, or advanced stage unless they had a contraindication or were intolerant to taxanes during or at the end of the first taxane cycle. Poly-ADP ribose polymerase (PARP) inhibitors were allowed as one of the two prior chemotherapies for patients with a documented germline BRCA1/BRCA2 mutation.

Patients were randomized 1:1 to receive TRODELVY (n=267) or Monochemotherapy of Physician's Choice (*Treatment of Physician's Choice,* TPC, n=262). TPC was determined by the investigator before randomization from one of the following single-agent regimens: eribulin (n=139), capecitabine (n=33), gemcitabine (n=38), or vinorelbine (except if patient had ≥ Grade 2 neuropathy, n=52). Patients with stable brain metastases were eligible. Magnetic resonance imaging (MRI) to determine brain metastases was required only for patients with known or suspected brain metastases. The study included a pre-defined maximum of 15% for patients with brain metastases; 468 patients enrolled did not have brain metastases and 61 patients enrolled had brain metastases. Patients with known Gilbert(-Meulengracht)'s syndrome, or bone-only disease were excluded.

Patients were administered either TRODELVY 10 mg/kg as an intravenous infusion on Days 1 and 8 of a 21-day treatment cycle or Monochemotherapy which was dosed based on body surface area and per the approved labeling. Prior to the administration of TRODELVY, all patients were administered a 2- or 3-drug combination regimen (e.g., dexamethasone with either a 5-HT3 receptor antagonist or a NK1 receptor antagonist and other drugs as indicated) for prevention and treatment of chemotherapy induced nausea and vomiting. All patients were given additional medications for prevention and treatment of nausea, vomiting, and diarrhea for use at home. Premedication, including antipyretics, H1 and H2 blockers, or corticosteroids (50 mg hydrocortisone or equivalent orally or IV), was strongly recommended to prevent infusion reactions with TRODELVY.

Patients were treated until disease progression or unacceptable toxicity. The primary efficacy endpoint was progression-free survival (PFS) in patients without brain metastases at baseline (i.e., BMNeg) as measured by a blinded, independent, centralized group of radiology experts using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 criteria. Secondary efficacy endpoints included PFS for the overall population, including all patients with and without brain metastases,

overall survival (OS) in both BMneg and overall population, objective response rate (ORR), duration of response (DOR), and time to response (TTR).

The primary analysis included 235 BMNeg patients in the TRODELVY group and 233 BMNeg patients in the control group. The overall demographics and baseline characteristics of the BMNeg patients were: median age of 54 years (range: 27–82 years); 99.6% female; 78.8% White; 12% Black/African American; 81% <65 years; median number of prior systemic therapies was 4.0; 70.5% had previously received 2 to 3 prior systemic therapies; 29.5% had previously received > 3 prior chemotherapies; 42.5% had hepatic metastases;
7.3% were BRCA1/BRCA2 mutational status positive. At study entry, all patients had an ECOG performance status of 0 (44%) or 1 (56%).

Overall, 27.1% of patients had received prior PD-1/PD-L1 therapy. Thirteen percent of patients in the TRODELVY group in the full population received only 1 prior line of systemic therapy in the metastatic setting.
The efficacy results in the brain metastases-negative population are summarized in Table 2.

Table 2: Efficacy Endpoints (Brain Metastases-Negative Population)

	TRODELVY n=235	**Treatment of Physician's Choice (Mono-chemotherapy) n=233**	**p-value*****	**Hazard Ratio (HR) or Odds Ratio (OR) (95% CI)*****
Median Progression-free Survival (PFS)*, ** Months (95% CI)	5.6 (4.3-6.3)	1.7 (1.5-2.6)	<0.0001	HR: 0.41 (0.32-0.52)
Median Overall Survival Months (95% CI)**	12.1 (10.7-14.0)	6.7 (5.8-7.7)	<0.0001	HR: 0.48 (0.38-0.59)
Objective Response Rate; n (%) - Complete Response - Partial Response	82 (35%) 10 (4%) 72 (31%)	11 (5%) 2 (1%) 9 (4%)	<0.0001	OR: 10.86 (5.59-21.10)
Median Duration of Response Months (95% CI)	6.3 (5.5-9.0)	3.6 (2.8-NE)	-	-

*PFS is defined as the time from the date of randomization to the date of the first radiological disease progression or death due to any cause, whichever comes first.

** Controlled for multiplicity statistical testing

*** For PFS and OS, P-values are based on stratified log-rank test; and HRs are from stratified Cox regression adjusted for stratification factors: number of prior chemotherapies (2-3 vs. >3), presence of known brain metastases at study entry (yes vs. no), and region (North America vs. rest of world). For ORR, P-value is based on Cochran–Mantel–Haenszel (CMH) test for common odds-ratio; and stratified odds-ratio is reported.

NE = not estimatable

The analysis of the overall population included 267 patients in the TRODELVY group (235 BMNeg patients and 32 patients with brain metastases) and 262 patients in the monochemotherapy group (233 BMNeg patients and 29 patients with brain metastases). The demographics and baseline characteristics of the BMNeg patients and overall population are similar.

The efficacy results in the overall population were consistent with the BMNeg population and are summarised in Table 3.

Table 3: Efficacy Endpoints (Overall Population) from ASCENT

	TRODELVY n = 267	Treatment of Physician's Choice (TPC) n = 262	p-value***	Hazard Ratio (HR) or Odds Ratio (OR) (95% CI)***
Median Progression-freeSurvival (PFS)*, ** Months (95% CI)	4.8 (4.1-5.8)	1.7 (1.5-2.5)	<0.0001	HR: 0.43 (0.35-0.54)
Median Overall SurvivalMonths (95% CI)**	11.8 (10.5-13.8)	6.9 (5.9-7.7)	<0.0001	HR: 0.51 (0.41-0.62)
Objective Response Rate; n (%) - Complete Response - Partial Response	83 (31%) 10 (4%) 73 (27%)	11 (4%) 2 (1%) 9 (3%)	<0.0001	OR: 10.99 (5.66-21.36)
Median Duration ofResponse Months (95% CI)	6.3 (5.5-9.0)	3.6 (2.8- NE)	-	-

* PFS is defined as the time from the date of randomization to the date of the first radiological disease progression or death due to any cause, whichever comes first.

** Controlled for multiplicity statistical testing

*** For PFS and OS, P-values are based on stratified log-rank test; and HRs are from stratified Cox regression adjusted for stratification factors: number of prior chemotherapies (2-3 vs. >3), presence of known brain metastases at study entry (yes vs. no), and region (North America vs. rest of world). For ORR, P-value is based on Cochran–Mantel–Haenszel (CMH) test for common odds-ratio; and stratified odds-ratio is reported.

NE = not estimatable

An exploratory analysis of PFS in patients with previously treated, stable brain metastases showed a stratified HR of 0.65 (95% CI: 0.35, 1.22). The median PFS in the TRODELVY arm was 2.8 months (95% CI: 1.5, 3.9) and the median PFS with monochemotherapy was 1.6 months (95% CI: 1.3, 2.9). Exploratory OS analysis in the same population showed a stratified HR of 0.87 (95% CI: 0.47, 1.63).

The median OS in the TRODELVY arm was 6.8 months (95% CI: 4.7, 14.1) and the median OS with monochemotherapy was 7.5 months (95% CI: 4.7, 11.1).

IMMU-132-01

The efficacy of TRODELVY was evaluated in a multicenter, single-arm, trial that enrolled 108 patients with metastatic triple-negative breast cancer (mTNBC) who had received at least two prior treatments for metastatic disease. Patients with bulky disease, defined as a mass > 7 cm, were not eligible. Patients with treated brain metastases not receiving high dose steroids (> 20 mg prednisone or equivalent) for at least four weeks were eligible. Patients with known Gilbert (-Meulengracht)'s syndrome were excluded.

Patients received TRODELVY 10 mg/kg intravenously on Days 1 and 8 of a 21-day treatment cycle. Patients were treated with TRODELVY until disease progression or intolerance to the therapy. Tumor imaging was obtained every 8 weeks, with confirmatory CT/MRI scans obtained 4-6 weeks after an initial partial or complete response, until progression requiring treatment discontinuation. Major efficacy outcome measures were investigator assessed overall response rate (ORR) using RECIST 1.1 and duration of response.

The median age was 55 years (range: 31 – 80 years); 82% of patients were younger than 65 years. The majority of patients were female (99%) and White (76%). At study entry, all patients had an ECOG performance status of 0 (29%) or 1 (71%).

The median number of prior systemic therapies received in the metastatic setting was 3 (range: 2 - 10).

Overall, 98% of patients had received prior taxanes and 86% had received prior anthracyclines either in the (neo)adjuvant or metastatic setting.

Table 4 summarizes the efficacy results.

Table 4: Efficacy results for patients with mTNBC in IMMU-132-01

	TRODELVY (N=108)
Overall Response Rate[i]	
ORR (95% CI)	33.3% (24.6%, 43.1%)
Complete response	2.8%
Partial response	30.6%
Response duration[i]	
Number of responders	36
Median, Months (95% CI)	7.7 (4.9, 10.8)
Range, Months	1.9+, 30.4+
% with duration ≥ 6 months	55.6%
% with duration ≥ 12 months	16.7%

[i] investigator assessment
CI: confidence interval
+: denotes ongoing

Elderly patients

Of the patients who received TRODELVY, 68/366 (18.6%) of patients with mTNBC and 185/660 (28%) of all patients were 65 years or older. Safety and efficacy were similar between these patients and younger patients with the exception of serious adverse events occurring in 41% of patients ≥ 65 years compared to 33% in patients between 50 and 64 years and 30% in patients < 50 years.

Pharmacokinetics

Absorption

The serum pharmacokinetics of sacituzumab govitecan and SN-38 were evaluated in study IMMU132-05 in mTNBC patients who received sacituzumab govitecan as a single agent at a dose of 10 mg/kg. The pharmacokinetic parameters of sacituzumab govitecan and free SN-38 are presented in Table 5.

Table 5: Summary of Mean PK Parameters (CV%) of Sacituzumab Govitecan and Free SN-38

	Sacituzumab govitecan	Free SN-38
C_{max} [ng/mL]	240000 (22.2%)	90.6 (65.0%)
AUC_{0-168} [ng*h/mL]	5340000 (23.7%)	2730 (41.1%)

C_{max}: maximum plasma concentration

AUC_{0-168}: area under plasma concentration curve through 168 hours

Distribution

Based on a population-based pharmacokinetic evaluation, the mean central volume of distribution for sacituzumab govitecan was 2.96 L.

Metabolism

No metabolism studies with sacituzumab govitecan have been conducted. SN-38 (the small molecule moiety of sacituzumab govitecan) is metabolized via UGT1A1. The glucuronide metabolite of SN-38 (SN-38G) was detectable in the serum of patients.

Elimination

The mean half-life of sacituzumab govitecan and free SN-38 was 15.3 and 19.7 hours, respectively. Based on a population-based pharmacokinetic analysis, the clearance of the sacituzumab govitecan was 0.14 L/h.

Linearity/non-linearity

Not applicable.

Kinetics in specific patient groups

A population-based pharmacokinetic analysis in patients treated with TRODELVY (n=527) did not find any effect of age or race on the pharmacokinetics of sacituzumab govitecan.

Hepatic impairment

The exposure of sacituzumab govitecan is similar in patients with mild hepatic impairment (bilirubin ≤ ULN and AST > ULN, or bilirubin > 1.0 to < 1.5 x ULN and AST of any level; n=59) to patients with normal hepatic function (bilirubin or AST < ULN; n=191).

Sacituzumab govitecan exposure is unknown in patients with moderate or severe hepatic impairment. SN-38 exposure may be elevated in such patients due to decreased hepatic UGT1A1 activity.

Renal impairment

A population-based pharmacokinetic analysis in patients treated with TRODELVY (n=527) did not find any effect of mild renal impairment on the pharmacokinetics of sacituzumab govitecan.
Renal elimination is known to contribute minimally to the excretion of SN-38, the small molecule moiety of sacituzumab govitecan. There are no data on the pharmacokinetics of sacituzumab

govitecan in patients with moderate or severe renal impairment or end-stage renal disease (ClCr ≤ 15 mL/min).

Genetic polymorphisms

SN-38 is metabolized via UGT1A1 (see “Properties/effects”). Genetic variants of the UGT1A1 gene such as the UGT1A1*28 allele lead to reduced UGT1A1 enzyme activity. Individuals who are homozygou s for the UGT1A1*28 allele are at increased risk for neutropenia, febrile neutropenia, and anemia from TRODELVY (see “Warnings and Precautions”). Approximately 20% of the Black or African American population, 10% of the White population, and 2% of the East Asian population are homozygous for the UGT1A1*28 allele. Decreased function alleles other than UGT1A1*28 may be present in certain populations.

Preclinical data

Genotoxicity

SN-38 was clastogenic in an *in vitro* mammalian cell micronucleus test in Chinese hamster ovary cells and was not mutagenic in an *in vitro* bacterial reverse mutation (Ames) assay.

Carcinogenicity

Carcinogenicity studies have not been conducted with sacituzumab govitecan.

Reproductive toxicity

There were no reproductive and developmental toxicology studies conducted with sacituzumab govitecan. Embryotoxicity, fetotoxicity, and teratogenicity were observed in rat or rabbit toxicity studies with Irinotecan. Fertility studies with sacituzumab govitecan have not been conducted. In a repeat-dose toxicity study in cynomolgus monkeys, intravenous administration of sacituzumab govitecan on Day 1 and Day 4 resulted in endometrial atrophy, uterine hemorrhage, increased follicular atresia of the ovary, and atrophy of vaginal epithelial cells at doses ≥ 60 mg/kg (≥ 6 times the human recommended dose of 10 mg/kg based on body weight).

Other information

Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products except those mentioned under “Instructions for handling”.

Shelf life

Do not use this medicine after the expiry date (“EXP”) stated on the pack.

Shelf life after opening

The reconstituted and diluted preparation for infusion is not preserved. Chemical and physical in-use stability after reconstitution and dilution has been demonstrated for 4 hours 2-8°C when protected from light (see “Instructions for handling”). For microbiological reasons, the ready-to-use preparation should be used immediately after reconstitution and dilution.

Special precautions for storage

Store in the refrigerator (2-8°C). Do not freeze.

Keep the vial in the outer carton in order to protect the content from light.

Keep out of the reach of children.

Instructions for handling

Preparation for Administration

Reconstitution

- TRODELVY is a cytotoxic drug.
- Follow applicable special handling and disposal procedures.
- Calculate the required dose (mg) of TRODELVY based on the patient’s body weight at the beginning of each treatment cycle (or more frequently if the patient’s body weight changed by more than 10% since the previous administration) (see “Dosage/Administration”).
- Allow the required number of vials to warm to room temperature.
- Using a sterile syringe, slowly inject 20 mL of a sterile 0.9% sodium chloride solution into each 180 mg TRODELVY vial. The resulting concentration will be 10 mg/mL.
- Gently swirl vials and allow to dissolve for up to 15 minutes. Do not shake. The solution should be free of visible particulates, clear and yellow. Do not use the reconstituted solution if it is cloudy or discolored.
- Use immediately to prepare a diluted TRODELVY infusion solution.

Dilution

- For the infusion to the patient the reconstituted TRODELVY must be diluted in 0.9% sodium chloride solution for infusion. Compatible infusions bags must consist of polyvinyl chloride, polypropylene, or ethylene propylene copolymer.
- Calculate the required volume of the reconstituted TRODELVY solution needed to obtain the appropriate dose according to patient’s body weight.
- Determine the final volume of the infusion solution to deliver the appropriate dose at a TRODELVY concentration range of 1.1 mg/mL to 3.3 mg/mL.
- Withdraw and discard a volume of 0.9% sodium chloride from the infusion bag (polyvinyl chloride, polypropylene, or ethylene propylene copolymer infusion bag) that is necessary to

achieve the indicated TRODELVY concentration following addition of the pre-determined volume of reconstituted TRODELVY solution.

- Withdraw the calculated amount of the reconstituted TRODELVY solution from the vial(s) using a syringe. Discard any unused portion remaining in the vial(s).
- To minimize foaming, slowly inject the required volume of reconstituted TRODELVY solution into a polyvinyl chloride, polypropylene, or ethylene propylene copolymer infusion bag. Do not shake the contents.
- If necessary, adjust the volume in the infusion bag as needed with a sterile 0.9% sodium chloride solution to obtain a concentration of 1.1 mg/mL to 3.3 mg/mL (total volume should not exceed 500 mL). Only 0.9% sodium chloride solution should be used since the stability of the reconstituted product has not been determined with other infusion-based solutions.
- For patients whose body weight exceeds 170 kg, divide the total dosage of TRODELVY equally between two 500 mL infusion bags and infuse sequentially via slow infusion.
- If not used immediately, the infusion bag containing TRODELVY solution can be stored refrigerated 2°C to 8°C for up to 4 hours protected from light. After refrigeration, administer diluted solution within 4 hours (including infusion time). The infusion bag must be protected from light.

Do not freeze or shake.

Authorisation number

68179 (Swissmedic).

Packs

Vials containing 180 mg: 1. [A]

Marketing authorisation holder

Gilead Sciences Switzerland Sàrl, Zug.

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