PRESCRIBING INFORMATION

TRODELVY® POWDER FOR SOLUTION FOR INFUSION 180 MG/VIAL

1. DESCRIPTION

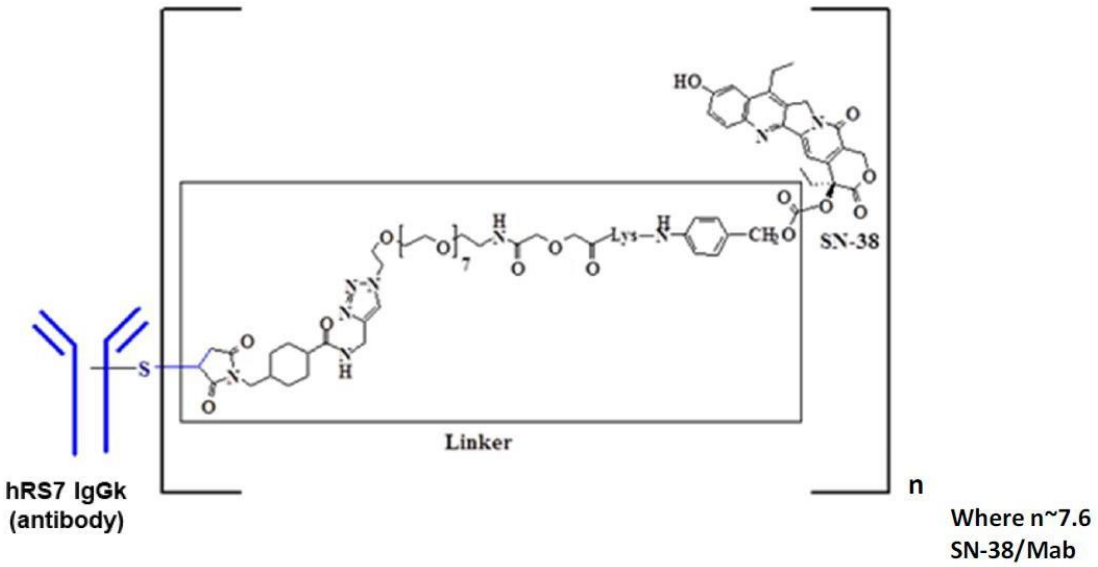
TRODELVY (sacituzumab govitecan) Powder for Solution for Infusion is a sterile, preservative-free, off-white to yellowish lyophilized powder for intravenous use in a 50 mL clear glass single-dose vial, with a rubber stopper and crimp-sealed with an aluminium flip-off cap.

Each single-dose vial of TRODELVY delivers 180 mg sacituzumab govitecan, 77.3 mg 2-(N-morpholino) ethane sulfonic acid (MES), 1.8 mg polysorbate 80 and 154 mg trehalose dihydrate. Reconstitution with 20 mL of 0.9% Sodium Chloride Injection, USP, results in a concentration of 10 mg/mL with a pH of approximately 6.5.

Sacituzumab govitecan is a Trop-2 directed antibody and topoisomerase inhibitor conjugate, composed of the following three components:

- the humanized monoclonal antibody, hRS7 IgG1κ (also called sacituzumab), which binds to Trop-2 (the trophoblast cell-surface antigen-2);
- the drug SN-38, a topoisomerase inhibitor;
- a hydrolysable linker (called CL2A), which links the humanized monoclonal antibody to SN-38.

The recombinant monoclonal antibody is produced by mammalian (murine myeloma) cells, while the small molecule components SN-38 and CL2A are produced by chemical synthesis. Sacituzumab govitecan contains on average 7 to 8 molecules of SN-38 per antibody molecule. Sacituzumab govitecan has a molecular weight of approximately 160 kilodaltons. Sacituzumab govitecan has the following chemical structure.



2. INDICATIONS AND USAGE

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

3. DOSAGE AND ADMINISTRATION

3.1. Important Use Information

Do NOT substitute TRODELVY for or use with other drugs containing irinotecan or its active metabolite SN-38**.**

3.2. Recommended Dose and Schedule

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 (5.3)].*

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.

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, H1 and H2 blockers prior to infusion, and 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 NK_1 receptor antagonist, as well as other drugs as indicated).

3.3. Dose Modifications for Adverse Reactions

Infusion-related Reactions

Slow or interrupt the infusion rate of TRODELVY if the patient develops an infusion-related reaction. Permanently discontinue TRODELVY for life-threatening infusion-related reactions *[see Warnings and Precautions (5.3)]*

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 (5.1)]*		
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	25% dose reduction and administer granulocyte-colony stimulating factor (G-CSF)
	Second	50% dose reduction
	Third	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, 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 (5.2, 5.4)]*, OR Other Grade 3-4 non-hematologic toxicity persisting >48 hours despite optimal medical management, OR At time of scheduled treatment, Grade 3-4 non neutropenic hematologic or non-hematologic toxicity, which delays dose by 2 or 3 weeks for recovery to ≤ Grade 1	First	25% dose reduction
	Second	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

3.4. Preparation and Administration

Reconstitution

- TRODELVY is a hazardous drug.
- Follow applicable special handling and disposal procedures for hazardous drug.
- 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 and Administration (3.2)]*.
- Allow the required number of vials to warm to room temperature.

- Using a sterile syringe, slowly inject 20 mL of 0.9% Sodium Chloride Injection, USP, into each 180 mg TRODELVY vial. Each vial contains overfill to compensate for liquid loss during preparation and after reconstitution, the total resulting volume delivers a **concentration of 10 mg/mL**.
- Gently swirl vials and allow to dissolve for up to 15 minutes. Do not shake. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. 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

- Calculate the required amount of the reconstituted TRODELVY solution needed to obtain the appropriate dose according to the 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 3.4 mg/mL (the total volume should not exceed 500 mL for patients weighing less than or equal to 170 kg). For patients whose body weight exceeds 170 kg, divide the total calculated dose between two 500 mL infusion bags. The 2 bags should be infused sequentially over the total calculated infusion time of TRODELVY in order to deliver the full dose.
- Use 0.9% Sodium Chloride Injection, USP only since the stability of the reconstituted TRODELVY solution has not been determined with other infusion-based solutions. Use polyvinyl chloride, polypropylene or ethylene/propylene copolymer infusion bag.
- Withdraw and discard the volume of 0.9% Sodium Chloride Injection, USP from the final infusion bag that is necessary to achieve the indicated TRODELVY concentration following the addition of the calculated amount 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 calculated amount of reconstituted TRODELVY solution into the infusion bag. Do not shake the contents.
- If not used immediately, the infusion bag containing TRODELVY solution can be stored refrigerated at 2°C to 8°C for up to 24 hours protected from light. After refrigeration, administer diluted solution at room temperature up to 25°C within 8 hours (including infusion time).

Do Not Freeze or Shake.

Administration

- Administer TRODELVY as an intravenous infusion. Protect infusion bag from light. The infusion bag should be covered during administration to the patient until dosing is complete. It is not necessary to cover the infusion tubing or to use light-protective tubing during the infusion.
- 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 Injection, USP.

4. CONTRAINDICATIONS

TRODELVY is contraindicated in patients who have experienced a severe hypersensitivity reaction to TRODELVY *[see Warnings and Precautions (5.3)]*.

5. WARNINGS AND PRECAUTIONS

5.1. 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 and Administration (3.3)].*

5.2. Diarrhea

TRODELVY can cause severe diarrhea. Diarrhea occurred in 64% of all patients treated with TRODELVY. Grade 3 diarrhea occurred in 12% of all patients treated with TRODELVY. Neutropenic colitis occurred in 0.5% of patients.

Withhold TRODELVY for Grade 3-4 diarrhea at the time of scheduled treatment administration and resume when resolved to ≤ Grade 1 *[see Dosage and Administration (3.3)].*

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.

5.3. 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 (4)]*.

Hypersensitivity reactions within 24 hours of dosing occurred in 37% of patients treated with TRODELVY. Grade 3-4 hypersensitivity occurred in 1% of patients treated with TRODELVY. The incidence of hypersensitivity reactions leading to permanent discontinuation of TRODELVY was 0.4%.

Pre-infusion medication for patients receiving TRODELVY is recommended. Observe patients closely for hypersensitivity and infusion-related reactions during each TRODELVY infusion and for at least 30 minutes after completion of each infusion *[see Dosage and Administration (3.3)]*. Medication to treat such reactions, as well as emergency equipment, should be available for immediate use.

5.4. Nausea and Vomiting

TRODELVY is emetogenic. Nausea occurred in 67% of all patients treated with TRODELVY. Grade 3-4 nausea occurred in 5% of patients.

Vomiting occurred in 40% of all patients treated with TRODELVY. Grade 3-4 vomiting occurred in 3% of these patients.

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 and Administration (3.3)].*

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.

5.5. Increased Risk of Adverse Reactions in Patients with Reduced UGT1A1 Activity

SN-38 is metabolized predominantly by uridine diphosphate-glucuronosyl transferase (UGT1A1). It has been reported that patients who are homozygous (UGT1A1*6/*6 or UGT1A1*28/*28) or heterozygous (UGT1A1*6/*28) in allele UGT1A1*6, UGT1A1*28 of UGT may be at increased risk for serious adverse reactions (especially neutropenia) caused by reduced glucuronidation of SN-38. Added caution should be exercised when administering in such patients *[see Pharmacogenomics (10.4)]*. Patients homozygous for the UGT1A1*28 allele are also at increased risk for febrile neutropenia and anemia; and may be at increased risk for other adverse reactions when treated with TRODELVY.

The incidence of neutropenia and anemia was analyzed in 577 patients who received TRODELVY and had UGT1A1 genotype results. In patients homozygous for the UGT1A1 *28 allele (n=70), the incidence of Grade 3-4 neutropenia was 69%. In patients heterozygous for the UGT1A1*28 allele (n=246), the incidence of Grade 3-4 neutropenia was 48%. In patients homozygous for the wild-type allele (n=261), the incidence of Grade 3-4 neutropenia was 46% *[see Clinical Pharmacology (10.4)]*. In patients homozygous for the UGT1A1 *28 allele (n=70), the incidence of Grade 3-4 anemia was 24%. In patients heterozygous for the UGT1A1*28 allele (n=246), the incidence of Grade 3-4 anemia was 8%. In patients homozygous for the wild-type allele (n=261), the incidence of Grade 3-4 anemia was 10%.

Closely monitor patients with known reduced UGT1A1 activity for adverse reactions. Withhold or permanently discontinue TRODELVY based on severity of the observed adverse reactions in patients with evidence of acute early-onset or unusually severe adverse reactions, which may indicate UGT1A1 reduced function *[see Dosage and Administration (3.3)].*

5.6. 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 Clinical Pharmacology (10.1)* and *Nonclinical Toxicology (11.1)*]. Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TRODELVY and for 6 months after the last dose. 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 *[see Use in Specific Populations (8.1, 8.3)].*

6. ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the label:

- Neutropenia *[see Warnings and Precautions (5.1)]*
- Diarrhea *[see Warnings and Precautions (5.2)]*
- Hypersensitivity and Infusion-Related Reactions *[see Warnings and Precautions (5.3)]*
- Nausea and Vomiting *[see Warnings and Precautions (5.4)]*

6.1. Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The pooled safety population described in the Warnings and Precautions section reflect exposure to TRODELVY as a single agent in 660 patients from two studies, IMMU-132-01 and IMMU-132-05 (ASCENT) which included 366 patients with mTNBC who had received prior systemic chemotherapy for advanced disease. TRODELVY was administered as an intravenous infusion once weekly on Days 1 and 8 of 21-day treatment cycles at doses of 10 mg/kg until disease progression or unacceptable toxicity. Among the 660 patients treated with TRODELVY, the median duration of treatment was 4.1 months (range: 0 to 51 months). In this pooled safety population, the most common (> 25%) adverse reactions were nausea, neutropenia, diarrhea, fatigue, alopecia, anemia, vomiting, constipation, rash, decreased appetite and abdominal pain.

ASCENT Study

The safety of TRODELVY was evaluated in a randomized, active-controlled, open-label trial (ASCENT) in patients with mTNBC who had previously received a taxane and at least two prior therapies. Patients were randomized (1:1) to receive either TRODELVY (n=258) or single agent chemotherapy (n=224) and were treated until disease progression or unacceptable toxicity *[see Clinical Studies (12)]*. For patients treated with TRODELVY, the median duration of treatment was 4.4 months (range: 0 to 23 months).

Serious adverse reactions occurred in 27% of patients receiving TRODELVY. Serious adverse reactions in > 1% of patients receiving TRODELVY included neutropenia (7%), diarrhea (4%), and pneumonia (3%). Fatal adverse reactions occurred in 1.2% of patients who received TRODELVY, including respiratory failure (0.8%) and pneumonia (0.4%). TRODELVY was permanently discontinued for adverse reactions in 5% of patients. Adverse reactions leading to permanent discontinuation in $\geqslant$ 1 % of patients who received TRODELVY were pneumonia (1%) and fatigue (1%).

Adverse reactions leading to a treatment interruption of TRODELVY occurred in 63% of patients. The most frequent ($\geqslant$5%) adverse reactions leading to a treatment interruption were neutropenia (47%), diarrhea (5%), respiratory infection (5%), and leukopenia (5%).

Adverse reactions leading to a dose reduction of TRODELVY occurred in 22% of patients. The most frequent (>4%) adverse reactions leading to a dose reduction were neutropenia (11%) and diarrhea (5%).

Granulocyte-colony stimulating factor (G-CSF) was used in 44% of patients who received TRODELVY.

Table 2 and Table 3 summarize adverse reactions and select laboratory abnormalities, respectively, in the

ASCENT study.

Table 2: Adverse Reactions in ≥10% of Patients with mTNBC in ASCENT

Adverse Reaction	TRODELVY (n=258)		Single Agent Chemotherapy (n=224)	
	All Grades %	Grade 3 - 4 %	All Grades %	Grade 3 - 4 %
Blood and lymphatic system disorders				
Neutropenia[I]	64	52	44	34
Anemia[II]	40	9	28	6
Leukopenia[III]	17	11	12	6
Lymphopenia[IV]	10	2	6	2
Gastrointestinal disorders				
Diarrhea	59	11	17	1
Nausea	57	3	26	0.4
Vomiting	33	2	16	1
Constipation	37	0.4	23	0
Abdominal Pain	30	3	12	1
Stomatitis[V]	17	2	13	1
General disorders and administration site conditions				
Fatigue[VI]	65	6	50	9
Pyrexia	15	0.4	14	2
Infections and infestation				
Urinary tract infection	13	0.4	8	0.4
Upper respiratory tract infection	12	0	3	0
Investigations				
Alanine aminotransferase increased	11	1	10	1
Metabolism and nutrition disorders				
Decreased appetite	28	2	21	1
Hypokalemia	16	3	13	0.4
Hypomagnesaemia	12	0	6	0
Musculoskeletal and connective tissue disorders				
Back pain	16	1	14	2
Arthralgia	12	0.4	7	0
Nervous system disorders				
Headache	18	0.8	13	0.4
Dizziness	10	0	7	0
Psychiatric disorders				
Insomnia	11	0	5	0
Respiratory, thoracic and mediastinal disorders				
Cough	24	0	18	0.4
Skin and subcutaneous tissue disorders				
Alopecia	47	0	16	0

Adverse Reaction	TRODELVY (n=258)		Single Agent Chemotherapy (n=224)	
	All Grades %	Grade 3 - 4 %	All Grades %	Grade 3 - 4 %
Rash	12	0.4	5	0.4
Pruritus	10	0	3	0

*Single agent chemotherapy included one of the following single-agents: eribulin (n=139), capecitabine (n=33), gemcitabine (n=38), or vinorelbine (except if patient had ≥Grade 2 neuropathy, n=52).

Graded per NCI CTCAE v.5.0.

I. Including neutropenia and neutrophil count decreased

II. Including anemia, hemoglobin decreased, and red blood cell count decreased

III. Including leukopenia and white blood cell count decreased

IV. Including lymphopenia and lymphocyte count decreased

V. Including stomatitis, glossitis, mouth ulceration, and mucosal inflammation

VI. Including fatigue and asthenia

Table 3: Select Laboratory Abnormalities in >10% of Patients with mTNBC in ASCENT

Laboratory Abnormality	TRODELVY (n=258)		Single Agent Chemotherapy (n=224)	
	All Grades (%)	Grade 3 - 4 (%)	All Grades (%)	Grade 3 - 4 (%)
Decreased hemoglobin	94	9	57	6
Decreased leukocytes	86	41	53	25
Decreased neutrophils	78	49	48	36
Decreased lymphocytes	88	31	40	24
Decreased platelets	23	1.2	25	2.7

Study IMMU-132-01

The safety of TRODELVY was evaluated in a single-arm, open-label study (IMMU-132-01) in patients with mTNBC and other malignancies, which included 108 patients with mTNBC who had received at least two prior treatments for metastatic disease *[see Clinical Studies (14)]*. TRODELVY was administered as an intravenous infusion once weekly on Days 1 and 8 of 21-day treatment cycles at doses up to 10 mg/kg until disease progression or unacceptable toxicity. The median treatment duration in these 108 patients was 5.1 months (range: 0-51 months).

Serious adverse reactions occurred in 31% of the patients. Serious adverse reactions in >1% of patients receiving TRODELVY included febrile neutropenia (6%), vomiting (5%), nausea (3%), dyspnea (3%), diarrhea (4%), anemia (2%), pleural effusion, neutropenia, pneumonia, dehydration (each 2%).

TRODELVY was permanently discontinued for adverse reactions in 2% of patients. Adverse reactions leading to permanent discontinuation were anaphylaxis, anorexia/fatigue, headache (each 0.9%). Forty-five percent (45%) of patients experienced an adverse reaction leading to treatment interruption. The most common adverse reaction leading to treatment interruption was neutropenia (33%). Adverse reactions leading to dose reduction occurred in 33% of patients treated with TRODELVY, with 24% having

one dose reduction, and 9% with two dose reductions. The most common adverse reaction leading to dose reductions was neutropenia/febrile neutropenia.

Adverse reactions occurring in ⩾10% of patients with mTNBC in the IMMU-132-01 study are summarized in Table 4.

Table 4: Adverse Reactions in ≥10% of Patients with mTNBC in IMMU-132-01

Adverse Reaction	TRODELVY (n=108)	
	Grade 1-4 (%)	Grade 3-4 (%)
Any adverse REACTION	100	71
Gastrointestinaldisorders	95	21
Nausea	69	6
Diarrhea	63	9
Vomiting	49	6
Constipation	34	1
Abdominal pain[I]	26	1
Mucositis[II]	14	1
General disorders and administration site conditions	77	9
Fatigue[III]	57	8
Edema[IV]	19	0
Pyrexia	14	0
Blood and lymphatic system disorders	74	37
Neutropenia	64	43
Anemia	52	12
Thrombocytopenia	14	3
Metabolism and nutrition disorders	68	22
Decreased appetite	30	1
Hyperglycemia	24	4
Hypomagnesemia	21	1
Hypokalemia	19	2
Hypophosphatemia	16	9
Dehydration	13	5
Skin and subcutaneous tissue disorders	63	4
Alopecia	38	0
Rash[V]	31	3
Pruritus	17	0
Dry Skin	15	0
Nervous system disorders	56	4
Headache	23	1
Dizziness	22	0

Adverse Reaction	TRODELVY (n=108)	
	Grade 1-4 (%)	Grade 3-4 (%)
Neuropathy[VI]	24	0
Dysgeusia	11	0
Infections and infestations	55	12
Urinary Tract Infection	21	3
Respiratory Infection[VII]	26	3
Musculoskeletal and connective tissue disorders	54	1
Back pain	23	0
Arthralgia	17	0
Pain in extremity	11	0
Respiratory, thoracic and mediastinal disorders	54	5
Cough[VIII]	22	0
Dyspnea[IX]	21	3
Psychiatric disorders	26	1
Insomnia	13	0

Graded per NCI CTCAE v.4.0

[I.] Including abdominal pain, distention, pain (upper), discomfort, tenderness

[II.] Including stomatitis, esophagitis, and mucosal inflammation

[III.] Including fatigue and asthenia

[IV.] Including edema; and peripheral, localized, and periorbital edema

[V.] Including rash; maculopapular, erythematous, generalized rash; dermatitis acneiform; skin disorder, irritation, and exfoliation

[VI.] Including gait disturbance, hypoesthesia, muscular weakness, paresthesia, peripheral and sensory neuropathy

[VII.] Including lower and upper respiratory tract infection, pneumonia, influenza, viral upper respiratory infection, bronchitis and respiratory syncytial virus infection

[VIII.] Includes cough and productive cough

[IX.] Includes dyspnea and exertional dyspnea

Table 5: Laboratory Abnormalities Observed in ≥10% of Patients while Receiving TRODELVY

Laboratory Abnormality	TRODELVY (n=108)	
	All Grades (%)	Grade 3-4 (%)
Hematology		
Decreased hemoglobin	93	6
Decreased leukocytes	91	26
Decreased neutrophils	82	32
Increased activated partial thromboplastin time	60	12
Decreased platelets	30	3

Laboratory Abnormality	TRODELVY (n=108)	
	All Grades (%)	Grade 3-4 (%)
Chemistry		
Increased alkaline phosphatase	57	2
Decreased magnesium	51	3
Decreased calcium	49	3
Increased glucose	48	3
Increased aspartate aminotransferase	45	3
Decreased albumin	39	1
Increased alanine aminotransferase	35	2
Decreased potassium	30	3
Decreased phosphate	29	5
Decreased sodium	25	4.7
Increased magnesium	24	4
Decreased glucose	19	2

6.2. Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described below with the incidence of antibodies in other studies or to other sacituzumab govitecan products may be misleading.

The analysis of immunogenicity of TRODELVY in serum samples from 106 patients with mTNBC was evaluated using an electrochemiluminescence (ECL)-based immunoassay to test for anti-Sacituzumab govitecan antibodies. Detection of the anti-sacituzumab govitecan antibodies was done using a 3-tier approach: screen, confirm, and titer. Persistent anti-sacituzumab govitecan antibodies developed in 2% (2/106) of patients.

7. DRUG INTERACTIONS

7.1. Effect of Other Drugs 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 Warning and Precaution (5.5) and Clinical Pharmacology (10.3, 10.4)].* Avoid administering UGT1A1 inhibitors with TRODELVY.

UGT1A1 Inducers

Exposure to SN-38 may be substantially reduced in patients concomitantly receiving UGT1A1 enzyme inducers *[see Warning and Precaution (5.5) and Clinical Pharmacology (10.3, 10.4)]*. Avoid administering UGT1A1 inducers with TRODELVY.

8. USE IN SPECIFIC POPULATIONS

8.1. Pregnancy

Risk Summary

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, and is toxic to rapidly dividing cells *[see Clinical Pharmacology (10.1) and Nonclinical Toxicology (11.1)].* Advise pregnant women and females of reproductive potential of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 – 4% and 15 – 20%, respectively.

Data

Animal data

There were no reproductive and developmental toxicology studies conducted with Sacituzumab govitecan.

8.2. Lactation

Risk Summary

There is no information regarding the presence of Sacituzumab govitecan or SN-38 in human milk, the effects on the breastfed child, or the effects on milk production. 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.

8.3. Females and Males of Reproductive Potential

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to the initiation of TRODELVY.

Contraception

Females

TRODELVY can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*. Advise females of reproductive potential to use effective contraception during treatment with TRODELVY and for 6 months after the last dose.

Males

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.

Infertility

Females

Based on findings in animals, TRODELVY may impair fertility in females of reproductive potential *[see*

Nonclinical Toxicology (11.1)].

8.4. Pediatric Use
Safety and effectiveness of TRODELVY have not been established in pediatric patients.

8.5. Geriatric Use
Of the patients who received TRODELVY, 28% of all patients were ≥ 65 years old. No overall differences in safety and effectiveness were observed between these patients and younger patients.

8.6. Hepatic Impairment
No adjustment to the starting dosage is required when administering TRODELVY to patients with mild hepatic impairment *[see Clinical Pharmacology (10.3)]*.

The safety of TRODELVY in patients with moderate (total bilirubin > 1.5 to 3.0 × ULN) or severe (total bilirubin > 3.0 × upper limit of normal [ULN]) hepatic impairment has not been established. TRODELVY has not been tested in patients with AST or ALT > 3 ULN without liver metastases, or AST or ALT > 5 ULN with liver metastases. No recommendations can be made for the starting dosage in these patients.

9. OVERDOSAGE

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.

10.CLINICAL PHARMACOLOGY

10.1. Mechanism of Action
Sacituzumab govitecan is a Trop-2-directed antibody-drug 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.

ATC code: L01FX17.

10.2. Pharmacodynamics
The TRODELVY exposure-response relationships and pharmacodynamic time-course for efficacy have not been fully characterized.

Cardiac electrophysiology
The maximum mean change from baseline was 9.7 msec (the upper bound of the two-sided 90% confidence interval is 16.8 msec) at the recommended dose. A positive exposure-response relationship was observed between QTc increases and SN-38 concentrations.

10.3. Pharmacokinetics

The serum pharmacokinetics of sacituzumab govitecan and SN-38 were evaluated in study IMMU-132-05 in a population of 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 6.

Table 6: 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} [h ng/mL]	5340000 (23.7%)	2730 (41.1%)

C_{max}: maximum serum concentration
AUC_{0-168}: area under serum concentration curve through 168 hours

Distribution

Based on population pharmacokinetic analysis, the central volume distribution of sacituzumab govetican is 2.96 L.

Elimination

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

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.

Specific Populations

Pharmacokinetic analyses in patients treated with TRODELVY (n=527) did not identify an effect of age, race, or 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 renal impairment or end-stage renal disease (CLcr ≤30 mL/min).

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

Sacituzumab govitecan exposure is unknown in patients with moderate (total bilirubin > 1.5 to 3.0 × ULN) or severe (total bilirubin > 3.0 × ULN) hepatic impairment. SN-38 exposure may be elevated in such patients due to decreased hepatic UGT1A1 activity.

Drug Interaction Studies

No drug-drug interaction studies were conducted with sacituzumab govitecan or its components. Inhibitors or inducers of UGT1A1 are expected to increase or decrease SN-38 exposure, respectively *[see Drug Interactions (7)].*

10.4. Pharmacogenomics

SN-38 is metabolized via UGT1A1 *[see Clinical Pharmacology (10.3)].* Genetic variants of the UGT1A1 gene

such as the UGT1A1*6 and UGT1A1*28 allele lead to reduced UGT1A1 enzyme activity. It has been reported that patients who are homozygous (UGT1A1*6/*6 or UGT1A1*28/*28) or heterozygous (UGT1A1*6/*28) in allele UGT1A1*6, UGT1A1*28 of UGT may be at increased risk for serious adverse reactions (especially neutropenia) caused by reduced glucuronidation of SN-38. Individuals who are homozygous for the UGT1A1*28 allele are also at increased risk for febrile neutropenia and anemia from TRODELVY *[see Warnings and Precautions (5.5)].* 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 and UGT1A1*6 may be present in certain populations.

11.NONCLINICAL TOXICOLOGY

11.1. Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with sacituzumab govitecan.

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.

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).

12.CLINICAL STUDIES

ASCENT

Efficacy was evaluated in a multicenter, open-label, randomized study (ASCENT; NCT02574455) conducted in 529 patients with unresectable locally advanced or metastatic triple-negative breast cancer (mTNBC) who had relapsed after at least two prior chemotherapies for breast cancer (one of which could be in the neoadjuvant or adjuvant setting provided progression occurred within a 12-month period). All patients received previous taxane treatment in either the adjuvant, neoadjuvant, or advanced stage unless there was a contraindication or intolerance to taxanes during or at the end of the first taxane cycle. Magnetic resonance imaging (MRI) to determine brain metastases was required prior to enrollment for patients with known or suspected brain metastases. Patients with brain metastases were allowed to enroll up to a predefined maximum of 15% of patients in the ASCENT trial. Patients with known Gilbert's disease or bone-only disease were excluded.

Patients were randomized (1:1) to receive TRODELVY 10 mg/kg as an intravenous infusion on Days 1 and 8 of a 21-day (n=267) or physician's choice of single agent chemotherapy (n=262). Single agent chemotherapy was determined by the investigator before randomization from one of the following choices: eribulin (n=139), capecitabine (n=33), gemcitabine (n=38), or vinorelbine (n=52).

Patients were treated until disease progression or unacceptable toxicity. The major efficacy outcome was progression-free survival (PFS) in patients without brain metastases at baseline (i.e., BMNeg) as measured by a blinded, independent, centralized review assessed using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 criteria. Additional efficacy measures included PFS for the full population (all patients with

and without brain metastases) and overall survival (OS).

The median age of patients in the full population (n = 529) was 54 years (range: 27–82 years); 99.6% were female; 79% were White, 12% were Black/African American; and 81% of patients were < 65 years of age. All patients had an ECOG performance status of 0 (43%) or 1 (57%). Forty-two percent of patients had hepatic metastases, 9% were BRCA1/BRCA2 mutational status positive, and 70% were TNBC at diagnosis. Twelve percent had baseline brain metastases previously treated and stable (n=61; 32 on TRODELVY arm and 29 on single agent chemotherapy arm).

Overall, 29% 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 are summarized in Table 7 and are shown in Figure 1 and Figure 2. Efficacy results for the subgroup of patients who had received only 1 prior line of systemic therapy in the metastatic setting (in addition to having disease recurrence or progression within 12 months of neoadjuvant/adjuvant systemic therapy) were consistent with those who had received at least two prior lines in the metastatic setting.

Table 7: Efficacy Results from ASCENT

	All Randomized Patients	
	TRODELVY n=267	**Single Agent Chemotherapy n=262**
Progression-Free Survival[1] per BICR		
Disease Progression or Death (%)	190 (71%)	171 (65%)
Median PFS in months (95% CI)	4.8 (4.1, 5.8)	1.7 (1.5, 2.5)
Hazard ratio[2] (95% CI)	0.43 (0.35, 0.54)	
p-value	<0.0001	
Overall Survival		
Deaths (%)	179 (67%)	206 (79%)
Median OS in months (95% CI)	11.8 (10.5, 13.8)	6.9 (5.9, 7.6)
Hazard ratio[2] (95% CI)	0.51 (0.41, 0.62)	
p-value	<0.0001	

[1] 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.

[2] Stratified log-rank test adjusted for stratification factors: number of prior chemotherapies, presence of known brain metastases at study entry, and region.

CI = Confidence Interval

Figure 1: Kaplan-Meier Plot of PFS by BICR (All Randomized Patients) in ASCENT

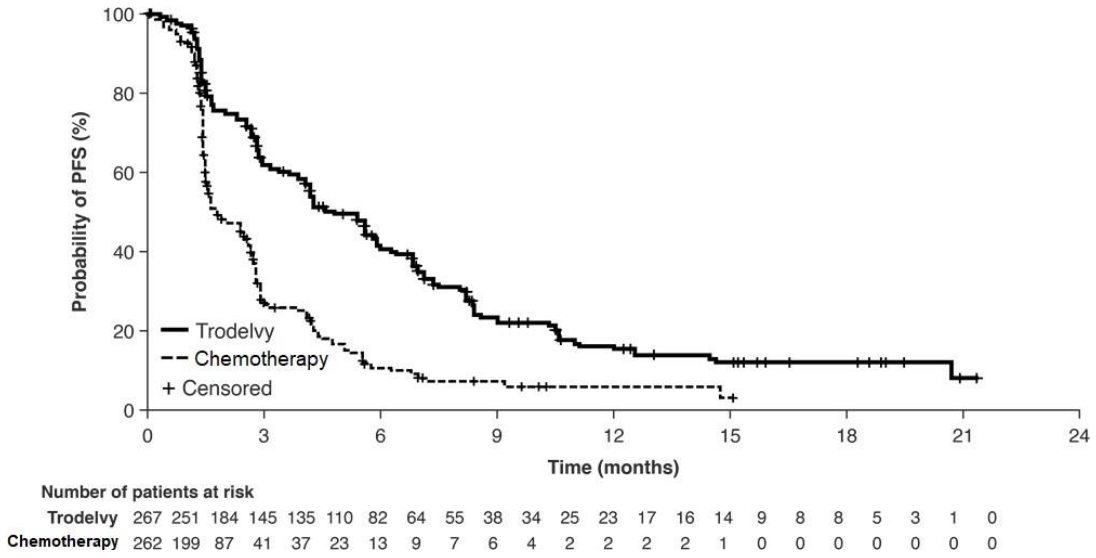
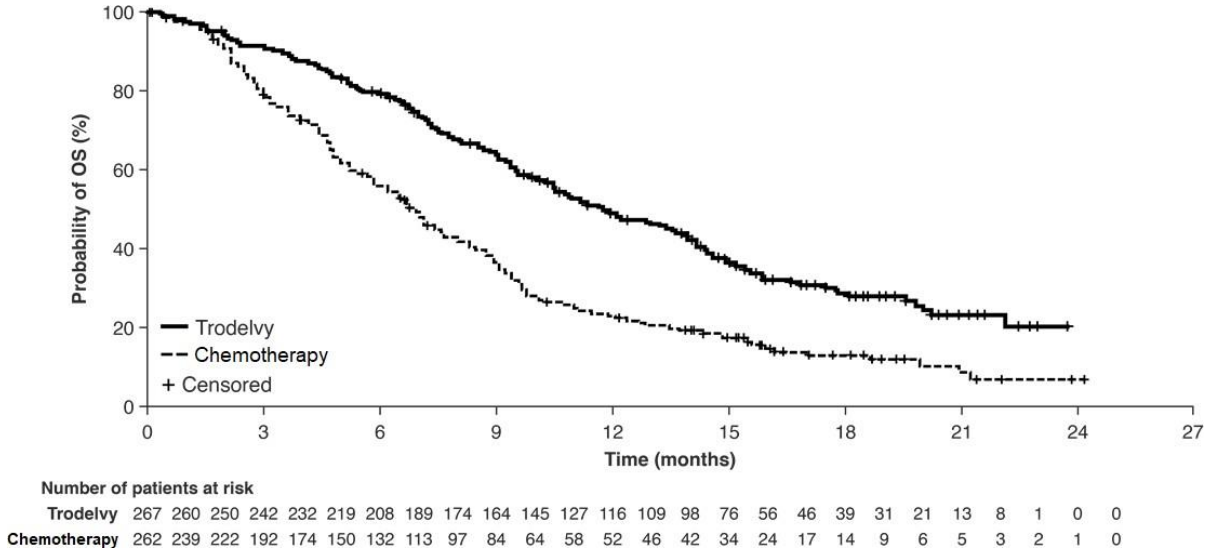


Figure 2: Kaplan-Meier Plot of OS (All Randomized Patients) in ASCENT



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 single agent chemotherapy 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 single agent chemotherapy was 7.4 months (95% CI: 4.7, 11.1).

IMMU-132-01

The efficacy of TRODELVY was evaluated in a multicenter, single-arm, trial (IMMU-132-01; NCT01631552) 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's disease 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 v1.1 and duration of response.

The median age was 55 years (range: 31 – 80 years); 87% 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%). Seventy-six percent had visceral disease, 42% had hepatic metastases, 56% had lung/pleura metastases, and 2% had brain metastases. Twelve patients (11%) had Stage IV disease at the time of initial diagnosis.

The median number of prior systemic therapies received in the metastatic setting was 3 (range: 2 - 10). Prior chemotherapies in the metastatic setting included carboplatin or cisplatin (69%), gemcitabine (55%), paclitaxel or docetaxel (53%), capecitabine (51%), eribulin (45%), doxorubicin (24%), vinorelbine (16%), cyclophosphamide (19%), and ixabepilone (8%).

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

Table 8 summarizes the efficacy results.

Table 8: 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

13.SHELF LIFE

See outer carton for expiry date.

Reconstituted solution should be diluted immediately with 0.9% Sodium Chloride Injection, USP.

If diluted solution is not used immediately, the infusion bag containing TRODELVY solution can be stored refrigerated at 2°C to 8°C for up to 24 hours protected from light. After refrigeration, administer diluted solution at room temperature up to 25°C within 8 hours (including infusion time).

14.SPECIAL PRECAUTIONS FOR STORAGE

Store vials in a refrigerator at 2°C to 8°C in the original carton to protect from light until time of reconstitution. Do not freeze.

TRODELVY is a hazardous drug. Follow applicable special handling and disposal procedures.

15.HOW SUPPLIED

Each vial contains 180 mg sacituzumab govitecan.

15.1. List of excipients

- 2-(N-morpholino) ethane sulfonic acid (MES) 77.3mg
- Polysorbate 80 1.8mg
- Trehalose dihydrate 154mg

No preservatives added.

15.2. Pack sizes

TRODELVY is supplied as single-vial carton containing 180 mg sacituzumab govitecan.

16.PRODUCT OWNER

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