FULL PRESCRIBING INFORMATION

1. NAME OF THE MEDICINAL PRODUCT

DATROWAY®

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains:
Datopotamab deruxtecan 100 mg powder for concentrate for solution for intravenous infusion.
Each vial is intended for reconstitution with 5 mL of Water for Injection to provide a solution of 20 mg/mL datopotamab deruxtecan.
For the full list of excipients, see section 11.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for intravenous infusion.

PATIENT SAFETY INFORMATION CARD

The marketing of Datroway is subject to a risk management plan (RMP) including a "patient safety information card". The patient safety information card emphasizes important safety information that the patient should be aware of before and during treatment. Please explain to the patient the need to review the card before starting treatment.

4. THERAPEUTIC INDICATIONS

DATROWAY is indicated for the treatment of adult patients with unresectable or metastatic, hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative (IHC 0, IHC 1+ or IHC

2+/ISH-) breast cancer who have received prior endocrine-based therapy and chemotherapy for unresectable or metastatic disease.

5. DOSAGE AND ADMINISTRATION

5.1 Recommended Dosage

The recommended dosage of DATROWAY is 6 mg/kg (up to a maximum of 540 mg for patients ≥90 kg) administered as an intravenous infusion once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity.

If a planned dose is delayed or missed, administer as soon as possible; do not wait until the next planned cycle. Adjust the schedule of administration to maintain a 3-week interval between doses.

5.2 Premedication, Concomitant Medications, and Required Eye Care

Administer DATROWAY in a setting where cardiopulmonary resuscitation medication and equipment are available

Conduct an ophthalmic exam including visual acuity testing, slit lamp examination (with fluorescein staining), intraocular pressure, and fundoscopy at initiation of DATROWAY, annually while on treatment, at end of treatment, and as clinically indicated.

Administer DATROWAY with the premedication and concomitant medications described in Table 1. Monitor patients for infusion-related reactions.

Monitor patients for at least 1 hour for the first 2 cycles of DATROWAY infusions. If there are no infusion-related reactions observed, monitor patients for at least 30 minutes for all subsequent cycles of infusions.

Table 1: Premedication and Concomitant Medications

Premedication [a]	**Examples (or equivalent)**	**Timing of Treatment/Duration**
Eye drops *[see Warnings and Precautions (8.2)]*	Preservative-free lubricant eye drops	Administer at least four times daily and as needed
Mouthwash *[see Warnings and Precautions (8.3)]*	Steroid-containing mouthwash (dexamethasone oral solution 0.1 mg/mL)	Administer four times daily and as needed

Antihistamine *[see Adverse Reactions (9.1)]*	Diphenhydramine (25 to 50 mg) administered intravenously or orally	Administer 30-60 minutes prior to each infusion
Antipyretic *[see Adverse Reactions (9.1)]*	Acetaminophen (650 to 1,000 mg) administered intravenously or orally	Administer 30-60 minutes prior to each infusion
Antiemetics *[see Adverse Reactions (9.1)]*	5-HT3 serotonin receptor antagonist or appropriate alternatives intravenously or oral	Prior to each infusion and thereafter as needed

[a] With or without systemic corticosteroids.

5.3 Dosage Modifications

Dosage Modifications for Adverse Reactions

The recommended dose reduction levels for adverse reactions are described in Table 2.

Table 2: Recommended Dosage Reductions of DATROWAY for Adverse Reactions

Dose Reductions	Recommended Dose
First	4 mg/kg (up to a maximum of 360 mg for patients ≥90 kg)
Second	3 mg/kg (up to a maximum of 270 mg for patients ≥90 kg)
Third	Permanently discontinue

Do not re-escalate the DATROWAY dose after a dose reduction. Permanently discontinue DATROWAY in patients who are unable to tolerate 3 mg/kg intravenously once every 3 weeks.

The recommended dosage modifications for adverse reactions of DATROWAY are described in Table 3.

Table 3: Dosage Modifications of DATROWAY for Adverse Reactions

Adverse Reaction	Severity [a]	Dosage Modifications
Interstitial Lung Disease (ILD)/Pneumonitis *[see Warnings and Precautions (8.1)]*	Asymptomatic ILD/pneumonitis Grade 1	Withhold DATROWAY until ILD/pneumonitis is completely resolved, then: • if resolved in ≤28 days, maintain current dose. • if resolved in >28 days, reduce one dose level (see Table 2). • Consider corticosteroids as soon as ILD/pneumonitis is suspected.
	Symptomatic ILD/pneumonitis Grade 2 or greater	• Permanently discontinue. • Administer corticosteroids as soon as ILD/pneumonitis is suspected.
Keratitis *[see Warnings and Precautions (8.2) and Adverse Reactions (9.1)]*	Nonconfluent superficial keratitis	• Monitor.
	Confluent superficial keratitis, a cornea epithelial defect, or 3-line or more loss	• Withhold until improved or resolved, then maintain at same dose level or consider dose reduction.

	in best corrected visual acuity	
	Corneal ulcer or stromal opacity or best corrected distance visual acuity 20/200 or worse	• Withhold until improved or resolved, then reduce by one dose level.
	Corneal perforation	• Permanently discontinue.
Stomatitis *[see Warnings and Precautions (8.3)]*	Grade 1	• Optimize prophylactic and supportive medications.
	Grade 2	• Withhold until resolved to < Grade 1. • Restart at the same dose level for first occurrence. • Consider restarting at reduced dose level (see Table 2) if recurrent.
	Grade 3	• Withhold until resolved to ≤Grade 1. • Restart at reduced dose level (see Table 2).
	Grade 4	• Permanently discontinue.
Infusion-Related Reactions (IRR) *[see Adverse Reactions (9.1)]*	Grade 1	• Reduce DATROWAY infusion rate by 50% if IRR is suspected and monitor patient closely.
	Grade 2	• Interrupt DATROWAY infusion and administer supportive care medications. • If the event resolves or improves to Grade 1, restart the infusion at 50% rate. • Administer all subsequent infusions at the reduced rate.
	Grade 3 or 4	• Permanently discontinue DATROWAY.
Other Non-Hematologic Adverse Reactions *[see Adverse Reactions (9.1)]*	Grade 3	• Withhold dose until resolved to ≤Grade 1 or baseline • Restart at reduced dose level (see Table 2).
	Grade 4	• Permanently discontinue DATROWAY.

[a] Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0.

5.4 Preparation and Administration

Reconstitute and further dilute DATROWAY prior to intravenous infusion. Use appropriate aseptic technique.

DATROWAY (datopotamab deruxtecan) is a cytotoxic drug. Follow applicable special handling and disposal procedures.

Reconstitution

- Reconstitute immediately before dilution.
- More than one vial may be needed for a full dose. Calculate the dose (mg), the total volume of reconstituted DATROWAY solution required, and the number of vial(s) of DATROWAY needed *[see Dosage and Administration (5.1)].*
- Reconstitute each 100 mg vial using a sterile syringe to slowly inject 5 mL of Sterile Water for Injection into each vial to obtain a final concentration of 20 mg/mL.
- Swirl the vial gently until completely dissolved. Do not shake.
- If not used immediately, refrigerate the reconstituted DATROWAY solution in the original vial at 2ºC to 8ºC for up to 24 hours from the time of reconstitution. Protect the vial from light. Do not freeze.
- The product does not contain a preservative. Discard unused reconstituted DATROWAY after 24 hours refrigerated.

Dilution

- Withdraw the calculated amount from the vial(s) using a sterile syringe. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. The reconstituted solution should be clear and colorless to light yellow. Do not use if visible particles are observed or if the solution is cloudy or discolored.
- Dilute the calculated volume of reconstituted DATROWAY in an infusion bag containing **100 mL of 5% Dextrose Injection.** DO NOT use Sodium Chloride Injection. DATROWAY is compatible with an infusion bag made of polyvinylchloride or polyolefin (polypropylene or copolymer of ethylene and propylene).
- Gently invert the infusion bag to thoroughly mix the solution. Do not shake.
- Cover the infusion bag to protect from light.
- If not used immediately, store at room temperature at up to 25ºC for up to 4 hours including preparation or in a refrigerator at 2ºC to 8ºC for up to 24 hours. Do not freeze.
- Discard any unused portion left in the vial.

Administration

- The maximum time from reconstitution of the vial through the end of administration should not exceed 24 hours. Discard if storage time exceeds these limits.
- If the prepared infusion solution was stored refrigerated at 2ºC to 8ºC, allow the solution to reach room temperature prior to administration, protected from light.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.
- Administer DATROWAY as an intravenous infusion only with an infusion line and tubing set made of polyvinyl chloride, polybutadiene or low-density polyethylene.
- Administer DATROWAY with a 0.2-micron in-line polytetrafluoroethylene, polyethersulfone or nylon 66 filter.
- Do NOT administer as an intravenous push or bolus.
- Cover the infusion bag to protect from light during administration.
- Do not mix DATROWAY with other drugs or administer other drugs through the same intravenous line.
- Instruct the patient to hold ice chips or ice water in the mouth throughout the infusion of DATROWAY.
- First infusion: Administer infusion over 90 minutes. Observe patients during the infusion and for at least 1 hour following the initial dose for signs or symptoms of infusion-related reactions.
- Second Infusion: If first infusion was tolerated, administer second infusion over 30 minutes. Observe patients during the infusion and for at least 1 hour after infusion.
- Subsequent Infusions: Administer infusion over 30 minutes if prior infusions were tolerated. Observe patients during the infusion and for at least 30 min after infusion.

6. DOSAGE FORMS AND STRENGTHS

Powder for concentrate for solution for intravenous infusion: 100 mg of datopotamab deruxtecan as a white to yellowish white, lyophilized powder in a single-dose vial for reconstitution and further dilution.

7. CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients listed in section 11.

8. WARNINGS AND PRECAUTIONS

8.1 Interstitial Lung Disease/Pneumonitis

DATROWAY can cause severe, life-threatening, or fatal interstitial lung disease (ILD) or pneumonitis.

In TROPION-Breast01, ILD/pneumonitis occurred in 4.2% of patients treated with DATROWAY, including 0.5% of patients with Grade 3-4 ILD/pneumonitis, and 0.3% with fatal ILD/pneumonitis. Six patients (1.7%) permanently discontinued DATROWAY due to ILD/pneumonitis. The median time-to-onset of ILD/pneumonitis was 3.5 months (range: 1.2 months to 10.8 months). Patients were excluded from TROPION-Breast01 for a history of ILD/pneumonitis requiring treatment with steroids or for ongoing ILD/pneumonitis.

Monitor patients for new or worsening respiratory symptoms indicative of ILD/pneumonitis (e.g., dyspnea, cough, fever) during treatment with DATROWAY. For asymptomatic (Grade 1) ILD/pneumonitis, consider corticosteroid treatment (e.g., ≥0.5 mg/kg/day prednisolone or equivalent). For symptomatic ILD/pneumonitis (Grade 2 or greater), promptly initiate systemic corticosteroid treatment (e.g., ≥1 mg/kg/day prednisolone or equivalent) and continue for at least 14 days followed by gradual taper for at least 4 weeks.

Withhold DATROWAY in patients with suspected ILD/pneumonitis and permanently discontinue DATROWAY if ≥Grade 2 ILD/pneumonitis is confirmed *[see Dosage and Administration (5.3)].*

8.2 Ocular Adverse Reactions

DATROWAY can cause ocular adverse reactions including dry eye, keratitis, blepharitis, meibomian gland dysfunction, increased lacrimation, conjunctivitis, and blurred vision.

In TROPION-Breast01, ocular adverse reactions occurred in 51% of patients treated with DATROWAY. Seven patients (1.9%) experienced Grade 3 ocular adverse reactions, including dry eye, keratitis, and blurred vision. The most common (≥5%) ocular adverse reactions were dry eye (27%), keratitis (24%), blepharitis and increased lacrimation (8% each), and meibomian gland dysfunction (7%). Patients with clinically significant corneal disease were excluded from TROPION-Breast01.

The median time to onset for ocular adverse reactions was 2.1 months (range: 0.03 months to 23.2 months). Of the patients who experienced ocular adverse reactions, 45% had complete resolution; 9% had partial improvement (defined as a decrease in severity by one or more grades from the worst grade at last follow up). Ocular adverse reactions led to permanent discontinuation of DATROWAY in 0.8% of patients.

Advise patients to use preservative-free lubricant eye drops several times daily for prophylaxis. Advise patients to avoid use of contact lenses unless directed by an eye care professional.

Refer patients to an eye care professional for an ophthalmic exam including visual acuity testing, slit lamp examination (with fluorescein staining), intraocular pressure, and fundoscopy at treatment initiation, annually while on treatment, at end of treatment, and as clinically indicated.

Promptly refer patients to an eye care professional for any new or worsening ocular adverse reactions. Monitor patients for ocular adverse reactions during treatment with DATROWAY, and if diagnosis is confirmed, dose delay, dose reduce, or permanently discontinue DATROWAY based on severity *[see Dosage and Administration (5.3)]*.

8.3 Stomatitis

DATROWAY can cause stomatitis, including mouth ulcers and oral mucositis.

In the TROPION-Breast01 study, stomatitis occurred in 59% of patients treated with DATROWAY, including 7% of patients with Grade 3-4 events. Median time to first onset was 0.7 months (range: 0.03 months to 8.8 months). Stomatitis led to interruption of DATROWAY in 1.9%, dosage reductions in 13%, and permanent discontinuation in 0.3% of patients.

In patients who received DATROWAY, 38% used a mouthwash containing corticosteroid for management or prophylaxis of stomatitis/oral mucositis at any time during the treatment.

Advise patients to use a steroid-containing mouthwash for prophylaxis and treatment of stomatitis. Instruct the patient to hold ice chips or ice water in the mouth throughout the infusion of DATROWAY.

Monitor patients for signs and symptoms of stomatitis. If stomatitis occurs, increase the frequency of mouthwash and administer other topical treatments as clinically indicated. Based on the severity of the adverse reaction, withhold, dose reduce, or permanently discontinue DATROWAY *[see Dosage and Administration (5.3)].*

8.4 Embryo-Fetal Toxicity

Based on its mechanism of action, DATROWAY can cause embryo-fetal harm when administered to a pregnant woman because the topoisomerase inhibitor component of DATROWAY, DXd *[see Description (11)]*, is genotoxic and affects actively dividing cells *[see Use in Specific Populations (10.1), Clinical Pharmacology (12.1), Nonclinical Toxicology (13.1)].*

Advise patients of the potential risk to a fetus. Advise female patients of reproductive potential to use effective contraception during treatment with DATROWAY and for 7 months after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with DATROWAY and for 4 months after the last dose *[see Use in Specific Populations (10.1, 10.3)].*

8.5 Effects on ability to drive and use machines

Datroway may influence the ability to drive and use machines. Patients should be advised to use caution when driving or operating machines in case they experience fatigue or vision changes during treatment with Datroway (see section 9).

8.6 Excipient with known effect
This medicine contains 1.5 mg of polysorbate 80 in each vial. Polysorbates may cause allergic reactions.

9. ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Interstitial Lung Disease/Pneumonitis *[see Warnings and Precautions (8.1)]*
- Ocular Adverse Reactions *[see Warnings and Precautions (8.2)]*
- Stomatitis *[see Warnings and Precautions (8.3)]*

9.1 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 practice.

Unresectable or Metastatic, HR-Positive, HER2-Negative Breast Cancer

TROPION-Breast01

The safety of DATROWAY was evaluated in 360 patients with unresectable or metastatic HR-positive, HER2-negative (IHC 0, IHC1+ or IHC2+/ISH-) breast cancer who received at least one dose of DATROWAY 6 mg/kg in TROPION-Breast01 [*see Clinical Studies (14.1)*]. DATROWAY was administered by intravenous infusion once every three weeks. The median duration of treatment was 6.7 months (range: 0.7 months to 16.1 months) for patients who received DATROWAY.

Serious adverse reactions occurred in 15% of patients who received DATROWAY. Serious adverse reactions in >0.5% of patients who received DATROWAY were urinary tract infection (1.9%), COVID-19 infection (1.7%), ILD/pneumonitis (1.1%), acute kidney injury, pulmonary embolism, vomiting, diarrhea, hemiparesis, and anemia (0.6% each). Fatal adverse reactions occurred in 0.3% of patients who received DATROWAY and were due to ILD/pneumonitis.

Permanent discontinuation of DATROWAY due to an adverse reaction occurred in 3.1% of patients. Adverse reactions which resulted in permanent discontinuation of DATROWAY in >0.5% of patients included ILD/pneumonitis (1.7%) and fatigue (0.6%).

Dosage interruptions of DATROWAY due to an adverse reaction occurred in 22% of patients. Adverse reactions which required dosage interruption in >1% of patients included COVID-19 (3.3%), infusion-related reaction (1.4%), ILD/pneumonitis (1.9%), stomatitis (1.9%), fatigue (1.7%), keratitis (1.4%), acute kidney injury (1.1%), and pneumonia (1.1%).

Dose reductions of DATROWAY due to an adverse reaction occurred in 23% of patients. Adverse reactions which required dose reduction in >1% of patients included stomatitis (13%), fatigue (3.1%), nausea (2.5%), and weight decrease (1.9%).

The most common (≥20%) adverse reactions, including laboratory abnormalities, were stomatitis, nausea, fatigue, decreased leukocytes, decreased calcium, alopecia, decreased lymphocytes, decreased hemoglobin, constipation, decreased neutrophils, dry eye, vomiting, increased ALT, keratitis, increased AST, and increased alkaline phosphatase.

Table 4: Adverse Reactions (≥10%) in Patients Who Received DATROWAY in TROPION-Breast01

Adverse Reactions	DATROWAY N=360		Chemotherapy N=351	
	All Grades %	Grades 3 or 4 %	All Grades %	Grades 3 or 4 %
Gastrointestinal Disorders				
Stomatitis [a]	59	7	17	2.6
Nausea	56	1.4	27	0.6
Constipation	34	0.3	17	0
Vomiting	24	1.1	12	1.1
Diarrhea	11	0.6	19	1.4
Abdominal pain [a]	11	0.6	15	1.4
General Disorders and Administration Site Conditions				
Fatigue [b]	44	4.2	40	3.7
Skin and Subcutaneous Tissue Disorders				
Alopecia	38	0	22	0
Rash [a]	19	0	17	2.3
Eye Disorders				
Dry eye	27	0.8	13	0
Keratitis [c]	24	1.1	10	0
Metabolism and Nutrition Disorders				
Decreased appetite	16	1.4	16	0.9
Infections and Infestations				
COVID-19 [a]	16	1.4	13	0.9
Respiratory, Thoracic, and Mediastinal Disorders				
Cough [a]	15	0	10	0

Events were graded using NCI CTCAE v5.0.

[a] Includes other related terms.

[b] Includes fatigue, asthenia, lethargy, malaise

[c] Includes corneal disorder, corneal erosion, corneal infiltrates, corneal lesion, corneal toxicity, injury corneal, keratitis, keratopathy, punctate keratitis, and ulcerative keratitis

Clinically relevant adverse reactions occurring in <10% of patients who received DATROWAY included infusion-related reactions (including bronchospasm), ILD/pneumonitis, headache, pruritus, dry skin, dry mouth, conjunctivitis, blepharitis, meibomian gland dysfunction, blurred vision, increased lacrimation, photophobia, visual impairment, skin hyperpigmentation, and madarosis.

Table 5: Select Laboratory Abnormalities (≥20%) in Patients Who Received DATROWAY in TROPION-Breast01

Laboratory Abnormality	DATROWAY [a]		Chemotherapy [a]	
	All Grades %	Grades 3-4 %	All Grades %	Grades 3-4 %
Hematology				
Decreased leukocytes	41	1.1	63	18
Decreased lymphocytes	36	9	42	11
Decreased hemoglobin	35	2.8	51	4.4
Decreased neutrophils	30	1.6	61	35
Chemistry				
Decreased calcium	39	1.4	43	1.2
Increased AST	23	1.9	28	0.9
Increased ALT	24	1.7	31	0.6
Increased alkaline phosphatase	23	0.6	20	0.6

Frequencies were based on NCI CTCAE v5.0 grade-derived laboratory abnormalities.

[a] The denominator used to calculate the rate varied from 264 to 359 based on the number of patients with a baseline value and at least one post-treatment value.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il

10 USE IN SPECIFIC POPULATIONS

10.1 Pregnancy

Risk Summary

Based on its mechanism of action, DATROWAY can cause embryo-fetal harm when administered to a pregnant woman because the topoisomerase inhibitor component of DATROWAY, DXd, is genotoxic and affects actively dividing cells *[see Clinical Pharmacology (12.1), Nonclinical Toxicology (13.1)]*. There are no available data on the use of DATROWAY in pregnant women to inform a drug-associated risk. Advise patients of the potential risks to a fetus.

Data

Animal Data

There were no animal reproductive or developmental toxicity studies conducted with datopotamab deruxtecan.

10.2 Lactation

Risk Summary

There are no data regarding the presence of datopotamab deruxtecan or its metabolites 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 with DATROWAY and for 1 month after the last dose.

10.3 Females and Males of Reproductive Potential

DATROWAY can cause embryo-fetal harm when administered to a pregnant woman *[see Use in Specific Populations (10.1)]*.

Pregnancy Testing

Verify pregnancy status of females of reproductive potential prior to initiation of DATROWAY.

Contraception

Females
Advise females of reproductive potential to use effective contraception during treatment with DATROWAY and for 7 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 DATROWAY and for 4 months after the last dose *[see Nonclinical Toxicology (13.1)]*.

Infertility

Based on findings in animal toxicity studies, DATROWAY may impair male and female reproductive function and fertility. The effects on reproductive organs in animals were irreversible *[see Nonclinical Toxicology (13.1)]*.

10.4 Pediatric Use

Safety and effectiveness of DATROWAY have not been established in pediatric patients.

10.5 Geriatric Use

Of the 365 patients in TROPION-Breast01 treated with DATROWAY 6 mg/kg, 25% were ≥65 years of age and 5% were ≥75 years of age. Grade ≥3 and serious adverse reactions were more common in patients ≥65 years (42% and 25%, respectively) compared to patients <65 years (33% and 15%, respectively). In TROPION-Breast01, no other meaningful differences in safety or efficacy were observed between patients ≥65 years of age versus younger patients.

10.6 Renal Impairment

A higher incidence of ILD/pneumonitis has been observed in patients with mild and moderate renal impairment (creatinine clearance [CLcr] 30 to <90 mL/min) *[see Warnings and Precautions (8.1)]*. Monitor patients with renal impairment for increased adverse reactions, including respiratory reactions. No dosage adjustment is recommended in patients with mild to moderate renal impairment *[see Clinical Pharmacology (12.3)]*. The effect of severe renal impairment (CLcr <30 mL/min) on the pharmacokinetics of datopotamab deruxtecan or DXd is unknown.

10.7 Hepatic Impairment

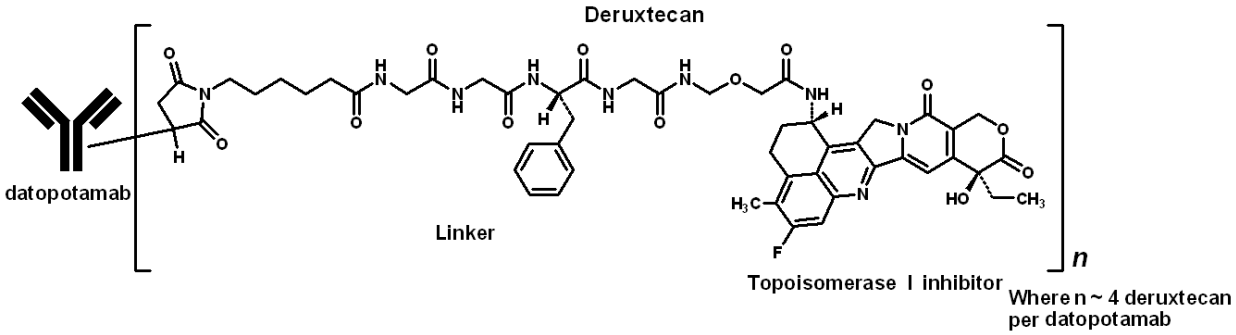
No dosage adjustment is recommended in patients with mild hepatic impairment (total bilirubin ≤ULN and any AST >ULN or total bilirubin >1 to 1.5 times ULN and any AST). Limited data are available in patients with moderate hepatic impairment (total bilirubin >1.5 to 3 times ULN and any AST). Monitor patients with moderate hepatic impairment for increased adverse reactions *[see Dosage and Administration (5.3)]*. The recommended dosage of DATROWAY has not

been established for patients with severe hepatic impairment (total bilirubin >3 times ULN and any AST) *[see Clinical Pharmacology (12.3)].*

11 DESCRIPTION

Datopotamab deruxtecan is a Trop2-directed antibody and topoisomerase inhibitor conjugate. Datopotamab deruxtecan is an antibody-drug conjugate (ADC) composed of three components: 1) a humanized anti-Trop2 IgG1 monoclonal antibody (mAb), covalently linked to 2) a topoisomerase I inhibitor, via 3) a tetrapeptide-based cleavable linker. Deruxtecan is composed of a protease-cleavable maleimide tetrapeptide linker and the topoisomerase inhibitor, DXd, which is an exatecan derivative.

The antibody is produced in Chinese hamster ovary cells by recombinant DNA technology, and the topoisomerase inhibitor and linker are produced by chemical synthesis. Approximately 4 molecules of deruxtecan are attached to each antibody molecule. Datopotamab deruxtecan has the following structure:



DATROWAY (datopotamab deruxtecan) Powder for concentrate for solution for intravenous infusion is a sterile, white to yellowish white, preservative-free lyophilized powder in single-dose vials. Each vial delivers 100 mg of datopotamab deruxtecan, polysorbate 80 (1.50 mg), L-histidine (3.88 mg), L-histidine hydrochloride monohydrate (5.25 mg), and sucrose (450 mg). Following reconstitution with 5 mL of Sterile Water for Injection, , the resulting concentration of datopotamab deruxtecan is 20 mg/mL with a pH of 6.0. The resulting solution is administered by intravenous infusion following dilution.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Datopotamab deruxtecan, is a Trop-2-directed antibody-drug conjugate. The antibody is a humanized anti-Trop2 IgG1. The small molecule, DXd, is a topoisomerase I inhibitor attached to the antibody by a cleavable linker. Following binding to Trop2 on cells, including tumor cells, datopotamab deruxtecan undergoes internalization and intracellular linker cleavage by lysosomal enzymes. Upon release, the membrane-permeable DXd causes DNA damage and apoptotic cell death. Datopotamab deruxtecan had anti-tumor activity in a mouse model of breast cancer.

12.2 Pharmacodynamics

Datopotamab deruxtecan time course of pharmacodynamic response is unknown.

Exposure-Response Relationships

A relationship between datopotamab deruxtecan exposure and efficacy has not been fully characterized in breast cancer.

Higher datopotamab deruxtecan systemic exposure is associated with a higher incidence rate of serious adverse reactions, dosage interruptions, dose reductions, stomatitis/oral mucositis, ocular adverse reactions, and Grade ≥3 adverse reactions.

Cardiac Electrophysiology

At datopotamab deruxtecan doses up to 10 mg/kg (1.7 times the recommended dose), mean increase in the QTc interval >20 ms was not observed.

12.3 Pharmacokinetics

Datopotamab deruxtecan and DXd exposure after the first dose of the approved recommended dosage of cycle 1 are provided in Table 6. Datopotamab deruxtecan and released DXd maximum concentration (C_{max}) and area under the time-concentration curve (AUC) increases proportionally over a dose range of 4 mg/kg to 10 mg/kg (approximately 0.7 to 1.7 times the approved recommended dosage). No clinically significant datopotamab deruxtecan accumulation occurs between cycles 1 and 3.

Table 6: Datopotamab Deruxtecan and DXd Mean (CV%) Exposure After the First Dose

PK Parameter	Datopotamab deruxtecan	DXd
C_{max}	154 µg/mL (20%)	2.8 ng/mL (58%)
AUC	671 µg*day/mL (31%)	18 ng*day/mL (43%)

Abbreviations: C_{max} =maximum concentration; AUC =area under the time-concentration curve

Distribution

Datopotamab deruxtecan mean steady state volume of distribution is 3.5 (23%) L.

DXd plasma protein binding is approximately 98% and the blood-to-plasma concentration ratio is 0.6 in vitro.

Elimination

The datopotamab deruxtecan median elimination half-life ($t_{1/2}$) is 4.8 days (1.0, 8.2) and the released DXd median apparent $t_{1/2}$ is approximately 5.5 days (3.2, 8.8). The estimated datopotamab deruxtecan clearance is 0.6 (31.5%) L/day.

Metabolism

Datopotamab deruxtecan undergoes intracellular cleavage by lysosomal enzymes to release DXd.

The humanized Trop-2 IgG1 monoclonal antibody is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG.

In vitro, DXd is primarily metabolized by CYP3A4.

Specific Populations

The mean volume of distribution and clearance of datopotamab deruxtecan and DXd increase with increasing body weight (36 kg to 156 kg).

No clinically significant differences in the pharmacokinetics of datopotamab deruxtecan or DXd were observed based on age (26 to 86 years), race (Asian, White, or Black), sex, mild hepatic impairment (total bilirubin ≤ULN and any AST >ULN or total bilirubin >1 to 1.5 times ULN and any AST), or mild to moderate renal impairment (CLcr 30 to <90 mL/min).

The pharmacokinetics of datopotamab deruxtecan in patients with moderate hepatic impairment (total bilirubin >1.5 to 3 times ULN and any AST) was comparable to patients with normal hepatic function (total bilirubin and AST ≤ULN). The steady state average DXd AUC was 2.4-fold higher in patients with moderate hepatic impairment compared to patients with normal hepatic function. The effect of severe hepatic impairment (total bilirubin >3 times ULN and any AST) or severe renal impairment (CLcr <30 mL/min) on datopotamab deruxtecan or DXd pharmacokinetics is unknown.

Drug Interaction Studies

Clinical Studies and Model-Informed Approaches
No clinically significant differences in DXd pharmacokinetics were predicted when used concomitantly with itraconazole (strong CYP3A inhibitor) or ritonavir (dual OATP1B and CYP3A inhibitor).

In Vitro Studies
CYP450 Enzymes: DXd does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A and does not induce CYP1A2, CYP2B6, or CYP3A.

UDP-Glucuronosyltransferase (UGT): DXd does not undergo significant metabolism by UGT enzymes.

Transporters Systems: DXd is a substrate of OATP1B1, OATP1B3, MATE2-K, P-gp, MRP1, and BCRP. DXd does not inhibit OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1, MATE2-K, P-gp, BCRP, or BSEP transporters.

12.6 Immunogenicity

There is insufficient information to characterize the anti-drug antibody response to datopotamab deruxtecan and the effects of anti-drug antibodies on pharmacokinetics, pharmacodynamics, safety, or effectiveness of datopotamab deruxtecan products.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with datopotamab deruxtecan.

The topoisomerase inhibitor component of datopotamab deruxtecan, DXd, was clastogenic in both an *in vivo* rat bone marrow micronucleus assay and an in vitro Chinese hamster lung chromosome aberration assay and was not mutagenic in an in vitro bacterial reverse mutation assay.

Dedicated fertility studies have not been conducted with datopotamab deruxtecan. In a 3-month repeat-dose toxicity study, intravenous administration of datopotamab deruxtecan once every 3 weeks in rats resulted in decreased weights in the testes and epididymides, degeneration of the germinal epithelium and atrophy of seminiferous tubules in testes, and cell debris, decreased number of sperm, and single-cell necrosis of the ductal epithelium in epididymides at 200 mg/kg (approximately 29 times the human recommended dose of 6 mg/kg based on AUC). Findings in female rats included increased atretic follicles in the ovary and single cell necrosis of mucosal epithelium in the vagina at 200 mg/kg. These findings, except for the lesions in the testis and epididymis, were not observed after a 2-month recovery period.

14 CLINICAL STUDIES

14.1 Unresectable or Metastatic, HR-Positive, HER2-Negative Breast Cancer

TROPION-Breast01

The efficacy of DATROWAY was evaluated in TROPION-Breast01 (NCT05104866), a multicenter, open-label, randomized trial of 732 patients with unresectable or metastatic HR-positive, HER2-negative (IHC 0, IHC1+ or IHC2+/ISH-) breast cancer. Eligible patients must have progressed on and deemed not suitable for further endocrine therapy. Patients were required to have received 1 or 2 lines of prior chemotherapy in the unresectable or metastatic disease setting. Patients were excluded for a history of ILD/pneumonitis requiring treatment with steroids, ongoing ILD/pneumonitis, clinically active brain metastases, or clinically significant corneal disease at screening. Patients were also excluded for ECOG performance status >1. Randomization was stratified by previous lines of chemotherapy (one or two), prior treatment with a CDK4/6 inhibitor (yes or no), and geographical region.

A total of 732 patients were randomized 1:1 to receive either DATROWAY 6 mg/kg (N=365) by intravenous infusion every 3 weeks or investigator's choice of chemotherapy (N=367) until unacceptable toxicity or disease progression. Single agent chemotherapy was determined by the investigator before randomization from one of the following choices: eribulin (60%), capecitabine (21%), vinorelbine (10%), or gemcitabine (9%).

The major efficacy outcomes were progression-free survival (PFS) as assessed by blinded independent central review (BICR) based on Response Evaluation Criteria in Solid Tumors (RECIST) v.1.1 and overall survival (OS). Additional efficacy outcomes included confirmed objective response rate (ORR) and duration of response (DOR) by BICR.

The median age was 55 years (range 28-86); 22% were ≥65 years; 99% were female; 48% were White, 41% were Asian, 1.5% were Black or African American, and 11% were of Hispanic/Latino ethnicity; 57% had ECOG PS of 0 and 42% had ECOG PS of 1; 97% had visceral disease, 72% had liver metastases, and 8% had stable brain metastases.
Sixty percent (60%) of patients received prior endocrine therapy in the (neo)adjuvant setting, and 89% received prior endocrine therapy in the unresectable or metastatic setting. Eighty-three percent (83%) of patients had prior treatment with a CDK4/6 inhibitor. All patients received prior chemotherapy regimens in the unresectable or metastatic setting (81% received prior taxanes; 64% received prior anthracyclines). Sixty-two percent (62%) of patients had 1 prior chemotherapy regimen and 38% of patients had 2 prior chemotherapy regimens for treatment of unresectable or metastatic disease.

The study demonstrated a statistically significant improvement in PFS in patients randomized to DATROWAY compared to chemotherapy.

Efficacy results are shown in Table 7 and Figure 1.

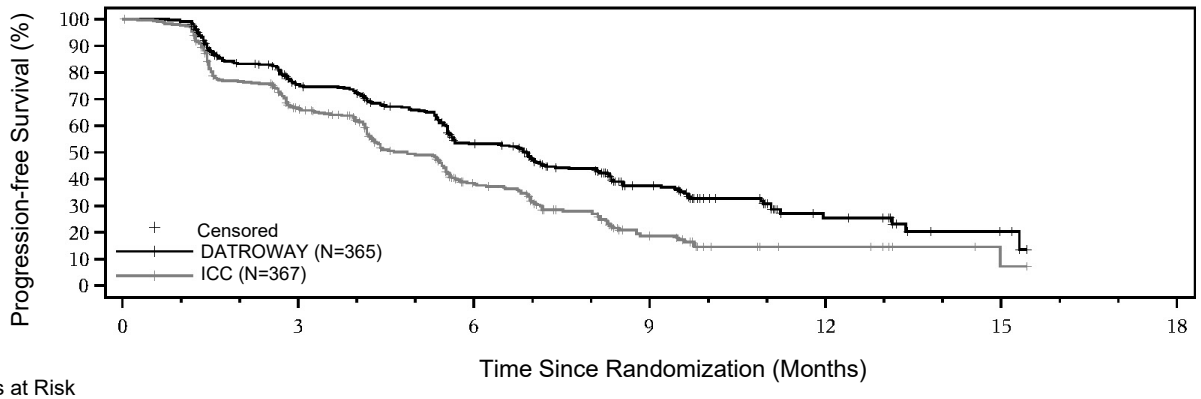
Table 7: Efficacy Results in TROPION-Breast01

	DATROWAY (n=365)	**Chemotherapy** (n=367)
Progression-Free Survival [a]		
Number of events (%)	212 (58)	235 (64)
Progressive Disease	201 (55)	218 (59)
Death	11 (3)	17 (5)
Median, months (95% CI)	6.9 (5.7, 7.4)	4.9 (4.2, 5.5)
Hazard ratio (95% CI) [b]	0.63 (0.52, 0.76)	
p-value [c, d]	< 0.0001	
Overall Survival		
Number of events (%)	223 (61)	213 (58)
Median, months (95% CI)	18.6 (17.3, 20.1)	18.3 (17.3, 20.5)
Hazard ratio (95% CI) [b]	1.01 (0.83, 1.22)	
p-value [c]	NS	
Confirmed Objective Response Rate [a]		
n (%)	133 (36)	84 (23)

(95% CI)	31, 42	19, 28
Complete Response n (%)	2 (0.5)	0
Partial Response n (%)	131 (36)	84 (23)
Duration of Response [a]		
Median, months (95% CI)	6.7 (5.6, 9.8)	5.7 (4.9, 6.8)

CI: Confidence interval; NS: not statistically significant
[a] Assessed by BICR
[b] Based on the stratified Cox proportional hazards model
[c] Two-sided p-value based on stratified log-rank test.
[d] p-value is compared with the allocated alpha of 0.01.

Figure 1: Kaplan-Meier Plot of PFS by BICR in TROPION-Breast-01



Numbers at Risk

DATROWAY (N=365)	365	249	158	66	15	4	0
ICC (N=367)	367	205	93	26	8	1	0

15. HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

DATROWAY (datopotamab deruxtecan) Powder for concentrate for solution for intravenous infusion is a white to yellowish white lyophilized powder supplied as one 100 mg single-dose vial

Storage and Handling
Store vials in a refrigerator at 2ºC to 8ºC in the original carton to protect from light until time of reconstitution. Do not freeze. Do not shake the reconstituted or diluted solution *[see Dosage and Administration (5.4)]*.

DATROWAY (datopotamab deruxtecan) is a cytotoxic drug. Follow applicable special handling and disposal procedures.[1]

16. REGISTRATION NUMBER:

180-45-38390-00

17. LICENSE HOLDER AND IMPORTER:

AstraZeneca (Israel) Ltd.,

1 Atirei Yeda St., P.O.B 8044, Kfar Saba 4464301

Approved on December 2025 according to MoH guidelines.