AusPAR - DATROWAY - datopotamab deruxtecan - PM-2024-01148-1-4 - AstraZeneca Pty Ltd - Type A
Date of Finalisation: 14 August 2025. This is the Product Information that was approved with the submission described in this AusPAR. It may have been superseded. For the most recent PI, please refer to the TGA website at < https://www.tga.gov.au/products/australian-register-therapeutic-goods-artg/product-information-pi>

▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION

DATROWAY® (datopotamab deruxtecan) powder for injection

1 NAME OF THE MEDICINE

Datopotamab deruxtecan.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial of lyophilised powder for concentrate for solution for infusion delivers 100 mg of datopotamab deruxtecan. After reconstitution, one vial of 5 mL solution delivers 20 mg/mL of datopotamab deruxtecan (see Section 4.2 Dose and method of administration).

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Powder for injection.

White to yellowish-white lyophilised powder.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Breast cancer

DATROWAY as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic hormone receptor (HR)-positive, HER2-negative (IHC 0, IHC 1+ or IHC 2+/ISH-) breast cancer who have received endocrine therapy and at least one additional systemic therapy in the locally advanced or metastatic setting.

4.2 DOSE AND METHOD OF ADMINISTRATION

Posology

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

First infusion: Administer infusion over 90 minutes. Observe patients during the infusion and for at least 30 minutes following the initial dose, for signs or symptoms of infusion-related reactions.

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

Premedication and prophylactic medications

Prior to each infusion of DATROWAY, a premedication regimen for the prevention of infusion-related reactions that consists of an antihistamine agent and paracetamol (with or without glucocorticoids) should be considered.

It is also recommended that patients receive prophylactic antiemetic agents (dexamethasone with 5-HT3 antagonists as well as other medicinal products, such as NK1 receptor antagonists), prior to infusion of DATROWAY and on subsequent days as needed.

For prophylactic treatment for keratitis and stomatitis, please refer to Section 4.4 Special warnings and precautions for use.

Dose modifications

Dose modifications for infusion-related reactions

Slow or interrupt the infusion rate if the patient develops an infusion-related reaction. Permanently discontinue DATROWAY for life-threatening infusion-related reactions.

Dose modifications for adverse reactions

Management of adverse reactions may require dose delay, dose reduction, or treatment discontinuation per guidelines provided in Tables 1 and 2.

Do not re-escalate the DATROWAY dose after a dose reduction is made.

Table 1. Dose reduction schedule

Recommended starting dose	6mg/kg (up to a maximum of 540 mg for patients ≥90 kg)
First dose reduction	4 mg/kg (up to a maximum of 360 mg for patients ≥90 kg)
Second dose reduction	3 mg/kg (up to a maximum of 270 mg for patients ≥90 kg)
Third dose reduction	Permanently discontinue

Table 2. Dosage modifications for adverse reactions

Adverse reaction	Severity[a]	Dose modification
Interstitial Lung Disease (ILD)/Pneumonitis (see Sections 4.4 and 4.7)	Asymptomatic ILD/pneumonitis Grade 1	Delay dose until resolved to Grade 0[b], then: • if resolved in 28 days or less from date of onset, maintain dose. • if resolved in greater than 28 days from date of onset, reduce dose one level (see Table 1). • consider corticosteroid treatment as soon as ILD/pneumonitis is suspected.
	Symptomatic ILD/pneumonitis (Grade 2 or greater)	• Permanently discontinue. • Promptly initiate corticosteroid treatment as soon as ILD/pneumonitis is suspected.
Keratitis (see Sections 4.4 and 4.7)	Grade 2	• Delay dose until resolved to Grade 1 or less, then maintain dose.
	Grade 3	• Delay dose until resolved to Grade 1 or less, then reduce the dose by 1 level (see Table 1).
	Grade 4	• Permanently discontinue.
	Grade 2	• Delay dose until resolved to Grade 1 or less.

Stomatitis (see Sections 4.4 and 4.7)		• Restart at the same dose for first occurrence. • Consider restarting at reduced dose level (see Table 1) if recurrent.
	Grade 3	• Delay dose until resolved to Grade 1 or less. • Restart at reduced dose level (see Table 1).
	Grade 4	• Permanently discontinue.
Infusion-Related Reactions (IRR) (see Section 4.8)	Grade 1	• Reduce infusion rate by 50% if IRR is suspected and monitor patient closely.
	Grade 2	• Interrupt 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.
Other Non-Haematologic Adverse Reactions (see section 4.8)	Grade 3	• Withhold dose until resolved to ≤Grade 1 or baseline • Restart at reduced dose level (see Table 1).
	Grade 4	• Permanently discontinue.

[a] Per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0

[b] Grade 0 refers to full resolution of ILD/pneumonitis, including the disappearance of radiological findings associated with active ILD/pneumonitis. Residual scarring or fibrosis following recovery of ILD/pneumonitis is not considered to be active disease.

Delayed or missed dose

If a planned dose is delayed or missed, it should be administered as soon as possible without waiting until the next planned cycle. The schedule of administration should be adjusted to maintain a 3-week interval between doses.

Special patient populations

Renal impairment

No dose adjustment is required in patients with mild to moderate (creatinine clearance [CLcr] 30 to <90 ml/min) renal impairment. The recommended dosage of DATROWAY has not been established in patients with severe renal impairment.

Hepatic impairment

No dose adjustment is required in patients with mild (total bilirubin ≤ULN and any AST >ULN or total bilirubin >1 to 1.5 times ULN and any AST) hepatic impairment. There are limited data to make a recommendation on dose adjustment in patients with moderate (total bilirubin >1.5 to 3 times ULN and any AST) hepatic impairment. Patients with moderate hepatic impairment should be monitored carefully for a potential increase in adverse reactions. The recommended dosage of DATROWAY has not been established for patients with severe (total bilirubin >3 times ULN and any AST) hepatic impairment (see section 5.2 Pharmacokinetic properties).

Use in the elderly

No dose adjustment of DATROWAY is required in patients aged 65 years or older.

Method of administration

DATROWAY is for intravenous use. It must be reconstituted and diluted by a healthcare professional and administered as an intravenous infusion. DATROWAY must not be administered as an intravenous push or bolus.

Appropriate procedures for the preparation of chemotherapeutic medicinal products should be used. Appropriate aseptic technique should be used for the following reconstitution and dilution 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.
- 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, store the reconstituted DATROWAY vials in a refrigerator at 2ºC to 8ºC for up to 24 hours, protected from light. Do not freeze.
- The product does not contain a preservative. Discard unused reconstituted DATROWAY after 24 hours refrigerated.

Dilution

Calculation to determine the volume of reconstituted DATROWAY (mL) to be further diluted:

$$\textbf{Reconstituted DATROWAY (mL)} = \frac{\text{DATROWAY dose (mg/kg) x patient's body weight (kg)}}{20\ \text{mg/mL}}$$

- Withdraw the calculated amount from the vial(s) using a sterile syringe. Inspect the reconstituted solution for particulates and discoloration. The solution should be clear and colourless to light yellow. Do not use if visible particles are observed or if the solution is cloudy or discoloured.
- Dilute the calculated volume of reconstituted DATROWAY in an infusion bag containing 100 mL of 5% dextrose solution. Do not use sodium chloride solution. DATROWAY is compatible with an infusion bag made of polyvinyl chloride (PVC), or polyolefin (polypropylene (PP), 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 for up to 4 hours including preparation and infusion or in a refrigerator at 2ºC to 8ºC for up to 24 hours, protected from light. 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 (2ºC to 8ºC), it is recommended that the solution be allowed to reach room temperature prior to administration, protected from light.
- Administer DATROWAY as an intravenous infusion only with an infusion line and tubing set made of PVC, polybutadiene (PBD), or low-density polyethylene (LDPE)
- Administer DATROWAY with a 0.2 micron in-line polytetrafluoroethylene (PTFE), polyethersulfone (PES) or nylon 66 filter.
- Do not administer as an intravenous push or bolus.
- Cover the infusion bag to protect from light.
- Do not mix DATROWAY with other medicinal products or administer other medicinal products through the same intravenous line.

4.3 CONTRAINDICATIONS

DATROWAY is contraindicated in patients who have experienced a severe hypersensitivity reaction to datopotamab deruxtecan or to any of the excipients (see Section 6.1 List of excipients).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Interstitial lung disease/pneumonitis

Cases of interstitial lung disease (ILD), including pneumonitis, have been reported in patients treated with DATROWAY (see Section 4.8 Adverse effects (Undesirable effects)). Fatal outcomes have been observed.

Patients should be advised to immediately report cough, dyspnea, fever, and/or any new or worsening respiratory symptoms. Patients should be monitored for signs and symptoms of ILD/pneumonitis. Evidence of ILD/pneumonitis should be promptly investigated. Patients with suspected ILD/pneumonitis should be evaluated by radiographic imaging. Consultation with a pulmonologist should be considered. For asymptomatic (Grade 1) ILD/pneumonitis, consider corticosteroid treatment (e.g., ≥0.5 mg/kg/day prednisolone or equivalent). DATROWAY should be delayed until recovery to Grade 0 and may be resumed according to instructions in Table 2 (see Section 4.2 Dose and method of administration). 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. DATROWAY should be permanently discontinued in patients who are diagnosed with symptomatic (Grade 2 or greater) ILD/pneumonitis (see Section 4.2 Dose and method of administration). Patients with a history of ILD/pneumonitis may be at increased risk of developing ILD/pneumonitis and should be monitored carefully.

In the breast cancer pooled patient population (see Section 4.8 Adverse effects (Undesirable effects)), ILD occurred in 2.9% of patients treated with DATROWAY 6 mg/kg, as determined by independent review. Most ILD cases were Grade 1 (1.1%) and Grade 2 (0.9%). Grade 3 ILD occurred in 0.7% of patients and no Grade 4 ILD were observed. Grade 5 ILD occurred in 0.2% of patients. Median time to first onset was 2.5 months (range: 1.1 to 8.3).

Adjudicated drug-related ILD was reported in the TB-01 DATROWAY arm only, in 15 (4.2%) patients. Two patients had Grade 3 pneumonitis. One patient had a Grade 5 pneumonitis. This event was assessed by the investigator as Grade 3 and death due to disease progression and was

subsequently assessed as fatal drug-related ILD by the Adjudication Committee. Six patients in the DATROWAY arm had study treatment discontinued (none in the ICC arm).

Ocular adverse reactions

DATROWAY can cause ocular surface events including keratitis. Signs and symptoms of keratitis may include dry eye, increased lacrimation, photophobia, and detrimental changes to vision (see (see Section 4.8 Adverse effects (Undesirable effects)). The majority of these events were mild to moderate in severity. Patients should be referred 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. Patients should be monitored for ocular adverse reactions during treatment with DATROWAY, and if diagnosis is confirmed, dose delay, dose reduce or permanently discontinue DATROWAY based on severity.

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. Promptly refer patients to an eye care professional for any new or worsening ocular signs and symptoms that could suggest keratitis. Monitor for keratitis and if diagnosis is confirmed, dose delay, dose reduce, or permanently discontinue DATROWAY (see Section 4.2 Dose and method of administration).

The overall rates of ocular surface toxicity were 51.4% in the DATROWAY arm, primarily due to dry eye (26.9%), keratitis (8.3%) and punctate keratitis (12.2%), blepharitis (7.8%) and meibomian gland dysfunction (6.9%), and lacrimation increased (7.8%).

Stomatitis

Stomatitis, including mouth ulcers and oral mucositis, have been reported in patients being treated with DATROWAY.

In addition to practicing good oral hygiene, when starting DATROWAY and throughout treatment, daily use of a steroid-containing mouthwash (e.g., dexamethasone oral solution 0.1 mg/mL 4 times daily or a similar steroid-containing mouthwash regimen) is recommended for prophylaxis and treatment. Where clinically indicated, antifungal agents may be considered in accordance with local guidelines. In the absence of a prophylactic steroid-containing mouthwash, use of bland mouth rinses (e.g., a non-alcoholic and/or bicarbonate-containing mouthwash) per local guidelines is recommended. Ice chips or ice water held in the mouth throughout the infusion may also be considered. If stomatitis does occur, frequency of mouthwashes may be increased and/or other topical treatments may be used. Based on the severity of the adverse reaction, dose delay, dose reduce, or permanently discontinue DATROWAY (see Section 4.2 Dose and method of administration).

In study TB-01 stomatitis occurred 60.0% of patients treated with DATROWAY, including 7.2% with grade 3 events. The majority of oral mucositis/stomatitis was Grade 1 or Grade 2. Dose reductions due to oral mucositis/stomatitis occurred in 13.6% of patients treated with DATROWAY and 2.8% had drug interrupted due to oral mucositis/stomatitis and 1 patient was discontinued from study treatment.

Embryo-fetal toxicity

Based on findings in animals and its mechanism of action, the topoisomerase I inhibitor component of DATROWAY can cause embryo-fetal harm when administered to a pregnant woman (see Section 4.6 Fertility, pregnancy and lactation).

The pregnancy status of females of reproductive potential should be verified prior to the initiation of DATROWAY. The patient should be informed of the potential risks to the fetus. Females of reproductive potential should be advised to use effective contraception during treatment and for at least 7 months following the last dose of DATROWAY. Male patients with female partners of reproductive potential should be advised to use effective contraception during treatment with DATROWAY and for at least 4 months after the last dose of DATROWAY (see Section 4.6 Fertility, pregnancy and lactation).

Use in the elderly

Of the 365 patients in TB-01 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).

Paediatric use

No data available.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Effects of other medicinal products on the pharmacokinetics of DATROWAY

In vitro studies indicate that the released topoisomerase I inhibitor is a substrate of the following transporters: P-glycoprotein (P-gp), OATP1B1, OATP1B3, MATE2K, MRP1, and BCRP. Inhibitors of these transporters could increase plasma concentrations of the released topoisomerase I inhibitor.

No clinical drug interaction studies with DATROWAY have been conducted. Based on PBPK modelling, coadministration with ritonavir, a dual inhibitor of OATP1B/CYP3A, or with itraconazole, a strong CYP3A inhibitor, is not predicted to have a clinically meaningful increase in exposures of datopotamab deruxtecan or released topoisomerase I inhibitor. No dose adjustment is required during coadministration of DATROWAY with drugs that are inhibitors of OATP1B or CYP3A.

No clinically meaningful interaction is expected with drugs that are inhibitors of P-glycoprotein (P-gp), MATE2-K, MRP1, or BCRP transporters.

Effects of DATROWAY on the pharmacokinetics of other medicinal products

In vitro studies indicate that topoisomerase I inhibitor does not inhibit or induce major CYP450 enzymes.

4.6 FERTILITY, PREGNANCY AND LACTATION

Women of childbearing potential

Pregnancy status of women of childbearing potential should be verified prior to initiation of DATROWAY.

Effects on fertility

No dedicated fertility studies have been conducted with datopotamab deruxtecan. Based on results from animal toxicity studies, DATROWAY may impair reproductive function and fertility.

In rats dosed with datopotamab deruxtecan every 3 weeks, atrophy of seminiferous tubules of testes, decreased number of spermatozoa and single cell necrosis of ductal epithelium in epididymides, and increased number of atretic follicles in ovaries and single cell necrosis of vaginal epithelium were observed at 200 mg/kg (approximately 29× the clinical AUC at the recommended clinical dose for datopotamab deruxtecan and 0.9× for the topoisomerase inhibitor). These findings, except for the lesions in the testis and epididymis, were not observed after a 2-month recovery period.

It is not known whether datopotamab deruxtecan or its metabolites are found in seminal fluid. Before starting treatment, male patients should be advised to seek counselling on sperm storage. Male patients must not freeze or donate sperm throughout the treatment period, and for at least 4 months after the final dose of DATROWAY. Females must not donate, or retrieve for their own use, ova throughout the treatment period and for at least 7 months after the final dose of DATROWAY.

Contraception in females and males

Women of childbearing potential should use effective contraception during treatment with DATROWAY and for at least 7 months following the last dose.

Men with female partners of childbearing potential should use effective contraception during treatment with DATROWAY and for at least 4 months following the last dose.

Use in pregnancy – Category D

There are no available data on the use of DATROWAY in pregnant women. However, based on findings in animals and its mechanism of action, the topoisomerase I inhibitor component of DATROWAY can cause embryo-fetal harm when administered to a pregnant woman (see Section 4.4 Special warning and precautions for use).

There were no animal reproductive or developmental toxicity studies conducted with datopotamab deruxtecan. Based on results from general animal toxicity studies, datopotamab deruxtecan and the topoisomerase I inhibitor component were toxic to rapidly dividing cells (lymphatic/haematopoietic organs, intestine, or testes), and the topoisomerase I inhibitor was genotoxic, suggesting the potential for embryo-fetal harm.

Administration of DATROWAY to pregnant women is not recommended, and patients should be informed of the potential risks to the fetus before they become pregnant. Women who become pregnant must immediately contact their doctor.

Use in lactation

It is not known if DATROWAY is excreted in human milk. Since many medicinal products are excreted in human milk and because of the potential for serious adverse reactions in breastfeeding infants, women should discontinue breastfeeding prior to initiating treatment with DATROWAY. Women may begin breastfeeding 1 month after concluding treatment.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

DATROWAY may have a minor influence on the ability to drive and use machines. Patients should be advised to use caution when driving or operating machinery in case they experience fatigue or vision changes during treatment with DATROWAY (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Breast cancer

HR+/HER2- Breast cancer

TROPION-Breast01 The safety of DATROWAY was evaluated in 360 patients with unresectable or metastatic breast cancer who received at least one dose of DATROWAY 6 mg/kg in TROPION-Breast01 (see Section 5.1 Pharmacodynamic properties, Clinical trials). DATROWAY was administered by intravenous infusion once every three weeks. The median duration of treatment was 6.7 months (range: 0.7 to 16.1) for patients who received DATROWAY and 4.1 months (range: 0.2 to 17.4) for patients who received chemotherapy.

Serious adverse reactions occurred in 3.1% of patients receiving DATROWAY. Serious adverse reactions in patients who received DATROWAY were ILD (1.1%), vomiting (0.6%), diarrhoea (0.6%), and anaemia (0.6%). Fatalities due to adverse reactions occurred in 0.3% of patients and were due to ILD.

DATROWAY was permanently discontinued in 2.5% of patients. The most frequent adverse reactions associated with discontinuation were ILD (1.4%) and fatigue (0.6%).

Dose interruptions due to adverse reactions occurred in 10.0% of patients treated with DATROWAY. The most frequent adverse reactions (≥1%) associated with dose interruption were fatigue (1.7%), stomatitis (1.7%), keratitis (1.4%), and infusion-related reactions (1.4%), and ILD (1.1%).

Dose reductions occurred in 18.6% of patients treated with DATROWAY. The most frequent adverse reactions (>2%) associated with dose reduction were stomatitis (13.3%), fatigue (3.1%), and nausea (2.5%).

The most common (≥20%) adverse reactions were stomatitis, nausea, fatigue, alopecia, constipation, dry eye, and vomiting.

Table 3. Common adverse reactions (≥10% all grades or ≥2% grades 3-4) in patients in TROPION-Breast01

	DATROWAY N = 360		Chemotherapy N = 351	
Adverse reactions	**All Grades %**	**Grade 3 or 4 %**	**All Grades %**	**Grade 3 or 4 %**
Blood and lymphatic system disorders				
Anaemia	15.6	2.5	24.5	3.4
Eye disorders				
Dry eye	24.2	0.6	13.1	0
Keratitis[a]	18.6	0.6	9.1	0
Gastrointestinal disorders				
Stomatitis[b]	58.6	6.9	17.4	2.6
Nausea	55.8	1.4	27.1	0.6
Constipation	33.6	0.3	17.1	0
Vomiting	23.9	1.1	11.7	1.1
Diarrhoea	10.6	0.6	18.8	1.4
General disorders and administration site conditions				
Fatigue[c]	44.4	4.2	39.6	13.7
Metabolism and nutrition disorders				
Decreased appetite	15.8	1.4	16.0	0.9
Skin and subcutaneous tissue disorders				
Alopecia	37.8	0	22.2	0
Rash[d]	13.1	0	3.7	0.3

Events were graded using NCI CTCAE version 5.0. N = number of patients.

[a] Including keratitis, punctate keratitis, ulcerative keratitis.

[b] Including stomatitis, aphthous ulcer, glossitis, mouth ulceration, odynophagia, oral pain, oropharyngeal pain, pharyngeal inflammation.

[c] Including fatigue, asthenia, lethargy, malaise.

[d] Including rash, erythematous rash, maculo-papular rash, pruritic rash.

Other clinically relevant adverse reactions reported in less than 10% of patients treated with DATROWAY in TROPION-Breast01:

- *Eye disorders:* conjunctivitis (9.4%), blepharitis (7.5%), lacrimation increased (7.2%), meibomian gland dysfunction (6.7%), blurred vision (3.6%), photophobia (0.8%), visual impairment (0.8%)
- *Gastrointestinal disorders:* dry mouth (5.3%)
- *Injury, poisoning and procedural complications:* infusion-related reaction (8.9%)
- *Respiratory, thoracic and mediastinal disorders:* interstitial lung disease (3.3%)
- *Skin and subcutaneous tissue disorders:* dry skin (6.4%), pruritus (6.1%), skin hyperpigmentation (4.4%), madarosis (1.9%)

Immunogenicity

There is insufficient information to characterise 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.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

There is no information on overdose with datopotamab deruxtecan. In the event of overdose, patients should be monitored, and appropriate supportive care should be given.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies and antibody drug conjugates

ATC code: L01FX35

Mechanism of action

Datopotamab deruxtecan, is a TROP2 directed antibody-drug conjugate (ADC). The antibody is a humanised anti-TROP2 IgG1 attached to deruxtecan, a topoisomerase I inhibitor bound by a tetrapeptide based cleavable linker. Following binding to TROP2 on tumour cells, datopotamab deruxtecan may undergo internalisation and intracellular linker cleavage by lysosomal enzymes that are upregulated in cancer cells. Upon release, the membrane permeable topoisomerase I inhibitor causes DNA damage and apoptotic cell death. Topoisomerase I inhibitor, an exatecan derivative, is approximately 10 times more potent than SN 38, the active metabolite of irinotecan.

Pharmacodynamic effects

The administration of doses of datopotamab deruxtecan ranging from 0.27 to 10 mg/kg did not show any clinically meaningful effect on the QTc interval in an open-label study in 195 patients with NSCLC.

Clinical trials

Breast cancer

HR+/HER2- Breast cancer

TROPION-Breast01

The efficacy of DATROWAY was evaluated in study TROPION-Breast01, a multicentre, open-label, randomised study of 732 patients with unresectable or metastatic HR-positive, HER2-negative (IHC 0, IHC1+ or IHC2+/ISH-) breast cancer. Patients must have progressed on and been unsuitable for endocrine therapy. Patients were required to have received 1 to 2 lines of prior chemotherapy in the unresectable or metastatic disease setting.

Patients with clinically inactive brain metastases were included in the study. Patients were excluded for a history of ILD/pneumonitis requiring treatment with steroids, ongoing ILD/pneumonitis, or clinically significant corneal disease at screening. Patients were also excluded for Eastern Cooperative Oncology Group (ECOG) performance status >1.

A total of 732 patients were randomised 1:1 to receive either DATROWAY 6 mg/kg (N=365) by intravenous infusion every 3 weeks or physician's choice of chemotherapy (N=367, eribulin 59.9%, capecitabine 20.7%, vinorelbine 10.4%, or gemcitabine 9.0%) until unacceptable toxicity or disease progression. Randomisation was stratified by previous lines of chemotherapy (one or two), prior treatment with a CDK4/6 inhibitor (yes or no), and geographical region. Tumour imaging was obtained every 6 weeks until disease progression.

The dual primary efficacy outcomes were progression-free survival (PFS) as assessed by blinded independent central review (BICR) based on Response Evaluation Criteria in Solid Tumours (RECIST) v.1.1 and overall survival (OS). Confirmed objective response rate (ORR), duration of response (DOR), and disease control rate (DCR) were secondary endpoints.

Baseline demographics and disease characteristics were similar between treatment arms. The median age was 55 years (range: 28–86); 22.3% were ≥65 years and 98.8% were female; 47.8% were White, 1.5% were Black or African American, 40.7% were Asian, and 11.3% were of Hispanic/Latino ethnicity; 57% had ECOG PS 0 and 42.3% had ECOG PS of 1; 97.3% had visceral disease, 71.9% had liver metastases, and 7.9% had stable brain metastases at baseline at the time of randomisation.

There were 60.2% of patients who received prior endocrine therapy in the (neo) adjuvant setting, 88.5% received prior endocrine therapy in the unresectable or metastatic setting, and all patients received prior chemotherapy regimens in the unresectable or metastatic setting. Overall, 80.7% of patients had received prior taxanes and 63.8% had received prior anthracyclines. There were 62.0% of patients who had 1 prior chemotherapy regimen and 37.7% of patients had 2 prior chemotherapy regimens for treatment of unresectable or metastatic disease. 82.5% of patients had prior treatment with a CDK4/6 inhibitor.

The study met its primary endpoint and demonstrated a statistically significant and clinically meaningful improvement in PFS in patients randomised to DATROWAY compared to chemotherapy. OS did not reach statistical significance at final analysis.

Efficacy results are shown in Table 4 and Figure 1.

Table 4. Efficacy results in TROPION-Breast01

Efficacy parameter	DATROWAY N=365	Chemotherapy N=367
Progression-free survival by BICR[a]		
Number of events (%)	212 (58.1)	235 (64.0)
Median, months (95% CI)	6.9 (5.7, 7.4)	4.9 (4.2, 5.5)
Hazard ratio (95% CI)	0.63 (0.52, 0.76)	
p-value[b]	< 0.0001	
Overall Survival[c, d]		
Number of events (%)	223 (61.1)	213 (58.0)

Median, months (95% CI)	18.6 (17.3, 20.1)	18.3 (17.3, 20.5)
Hazard ratio (95% CI)	1.01 (0.83, 1.22)	
p-value[e]	0.9445	
Objective response rate by BICR[a]		
n (%)	133 (36.4)	84 (22.9)
95% CI	31.4, 41.3	18.6, 27.2
Best objective response rate by BICR[a]		
Complete response n (%)	2 (0.5)	0
Partial response n (%)	131 (35.9)	84 (22.9)
Stable disease n (%)[f]	168 (46.0)	176 (48.0)
Duration of response by BICR[a]		
Median, months (95% CI)	6.7 (5.6, 9.8)	5.7 (4.9, 6.8)
Disease control rate by BICR[a, g]	275 (75.3)	234 (63.8)

[a] Data cutoff 17 July 2023.

[b] Predefined p-value boundary was 0.01.

[c] Data cutoff 24 July 2024.

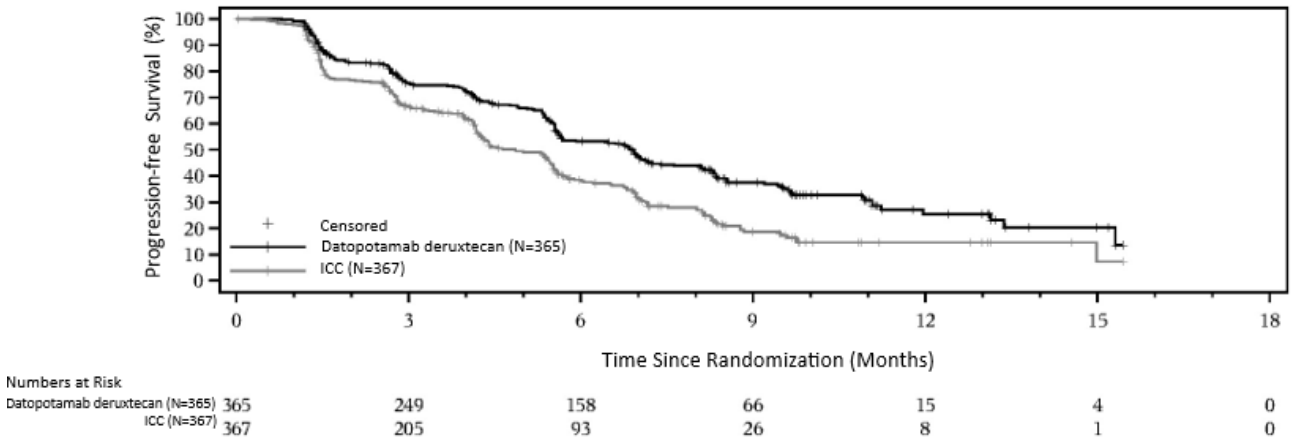
[d] 12.3% and 24.0% of patients in the datopotamab deruxtecan and ICC arms, respectively, received subsequent treatment with trastuzumab deruxtecan and/or sacituzumab govitecan post discontinuation

[e] Predefined p-value boundary was 0.0403.

[f] Stable disease was recorded ≥5 weeks after randomisation.

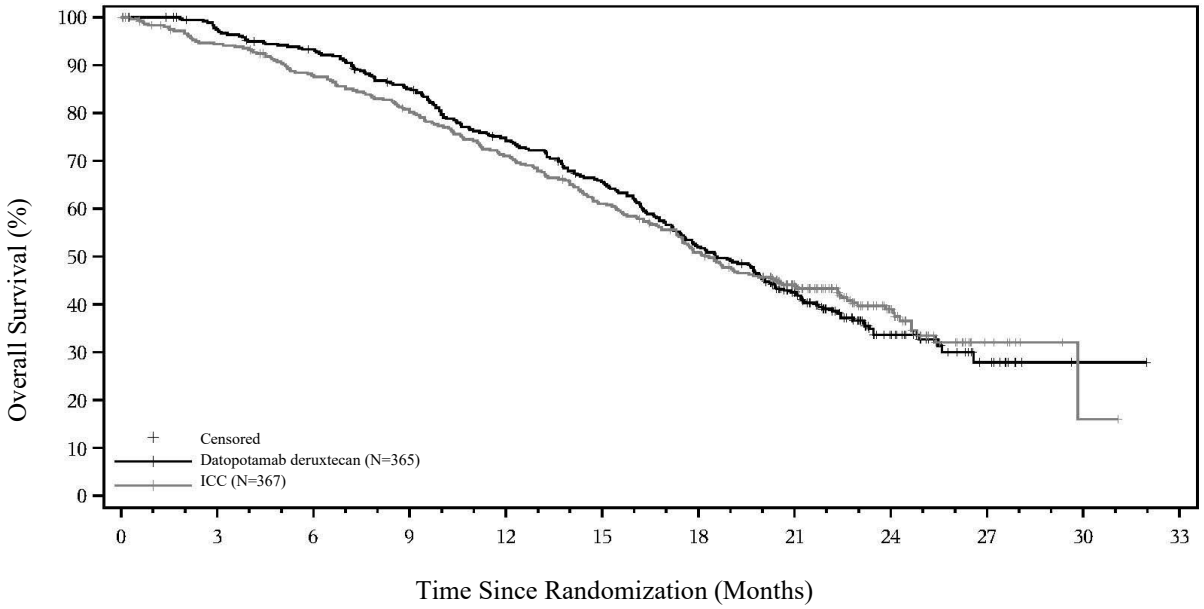
[g] Disease control rate at 12 weeks was defined as the percentage of subjects who have a confirmed CR or PR or have demonstrated SD for at least 11 weeks after randomisation without subsequent cancer therapy per RECIST v.1.1.

Figure 1. Kaplan-Meier Plot of PFS by BICR in TROPION-Breast01 (data cutoff 17 July 2023)



The improvement in PFS by BICR was consistent amongst the prespecified subgroups of patients including by geographic region, prior use of CDK4/6 inhibitor, and previous line of therapy.

Figure 2: Kaplan-Meier Plot of Final OS in TROPION-Breast01 (data cutoff 24 July 2024)



Number at risk												
Datopotamab deruxtecan (N=365)	365	349	331	299	259	227	180	118	49	12	1	0
ICC (N=367)	367	335	309	283	249	213	175	123	51	9	1	0

5.2 PHARMACOKINETIC PROPERTIES

At the recommended dosage of DATROWAY, the geometric mean (coefficient of variation [CV]%) C_{max} of datopotamab deruxtecan and topoisomerase I inhibitor were 154 µg/mL (20.3%) and 2.82 ng/mL (58.1%), respectively, and the corresponding AUC were 671 µg*day/mL (31.4%) and 18.5 ng*day/mL (42.6%) after the first dose in cycle 1.

Distribution

The steady state volume of distribution of datopotamab deruxtecan is 3.52 L.

In vitro, across the concentration range of 10 ng/mL to 100 ng/mL, the mean human plasma protein binding of topoisomerase I inhibitor was 96.8 to 98.0%, and the blood-to-plasma concentration ratio of topoisomerase I inhibitor was 0.59–0.62.

Metabolism

Datopotamab deruxtecan may undergo intracellular cleavage by lysosomal enzymes to release topoisomerase I inhibitor.

The humanised TROP2 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 metabolism studies in human liver microsomes indicate that topoisomerase I inhibitor is primarily metabolised by CYP3A4 via oxidative pathways and does not undergo significant metabolism by UGT or other CYP enzymes.

Excretion

The clearance of datopotamab deruxtecan was estimated to be 0.57 L/day. The median elimination half-life ($t_{1/2}$) of datopotamab deruxtecan was 4.82 days and apparent median $t_{1/2}$ of released topoisomerase I inhibitor was approximately 5.50 days. No accumulation of datopotamab deruxtecan was observed at the 6 mg/kg dose between cycle 1 and cycle 3.

Following intravenous administration of topoisomerase I inhibitor to rats and monkeys, the major excretion pathway was faeces via the biliary route. Topoisomerase I inhibitor was the most abundant component in urine, faeces, and bile.

Linearity/nonlinearity

The exposure of datopotamab deruxtecan and released topoisomerase I inhibitor when administered intravenously increased in proportion to dose in the 4 mg/kg to 10 mg/kg dose range (approximately 0.7 to 1.7 times the recommended dose).

Specific populations

Age, race, ethnicity, body weight, and sex

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

No clinically significant differences in the pharmacokinetics of datopotamab deruxtecan or topoisomerase I inhibitor were observed for age (26–86 years), race (Asian, White, or Black), and sex.

Renal impairment

No dedicated renal impairment study was conducted. Based on population pharmacokinetic analysis including patients with mild to moderate (creatinine clearance [CLcr] 30 to <90 ml/min) renal impairment, the pharmacokinetics of datopotamab deruxtecan or topoisomerase I inhibitor was not affected by mild to moderate renal impairment as compared to normal renal function (CLcr ≥90 mL/min). The effect of severe renal impairment (CLcr <30 mL/min) on datopotamab deruxtecan or DXd pharmacokinetics is unknown.

Hepatic impairment

No dedicated hepatic impairment study was conducted. Based on population pharmacokinetic analysis including patients with mild hepatic impairment (total bilirubin ≤ULN and any AST >ULN or total bilirubin >1 to 1.5 times ULN and any AST), the pharmacokinetics of datopotamab deruxtecan or topoisomerase I inhibitor was not affected by mild hepatic impairment as compared to normal hepatic function. The steady state average DXd AUC was 2.4-fold higher in patients with moderate (total bilirubin >1.5 to 3 times ULN and any AST) hepatic impairment compared to patients with normal hepatic function. The effect of severe hepatic impairment (total bilirubin >3 times ULN and any AST) on datopotamab deruxtecan or DXd pharmacokinetics is unknown.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

The topoisomerase I inhibitor component of datopotamab deruxtecan 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.

Carcinogenicity

Carcinogenicity studies have not been conducted with datopotamab deruxtecan.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Histidine, histidine hydrochloride monohydrate, sucrose, and polysorbate 80.

6.2 INCOMPATIBILITIES

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

Sodium chloride solution for infusion must not be used for reconstitution or dilution since it may cause particulate formation.

6.3 SHELF LIFE

Unopened vial

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

Reconstituted Solution

It is recommended that the reconstituted solution be used immediately. If not used immediately, the reconstituted solution may be stored in a refrigerator at 2ºC to 8ºC for up to 24 hours from the time of reconstitution, protected from light.

Diluted Solution

It is recommended that the diluted solution be used immediately. If not used immediately, the diluted solution may be stored at room temperature for up to 4 hours or in a refrigerator at 2ºC to 8ºC for up to 24 hours, protected from light.

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.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store vials in a refrigerator (2ºC to 8ºC) until time of reconstitution.

Do not freeze.

For storage conditions after reconstitution and dilution of the medicinal product, see Section 6.3 Shelf life.

6.5 NATURE AND CONTENTS OF CONTAINER

DATROWAY is provided in a 10 mL Type 1 amber borosilicate glass vial sealed with a fluoro-resin laminated butyl rubber stopper and a polypropylene/aluminium blue flip-off crimp cap.

Each carton contains 1 glass vial.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

The reconstituted product contains no preservative and is intended for single use only. Discard any unused portion left in the vial.

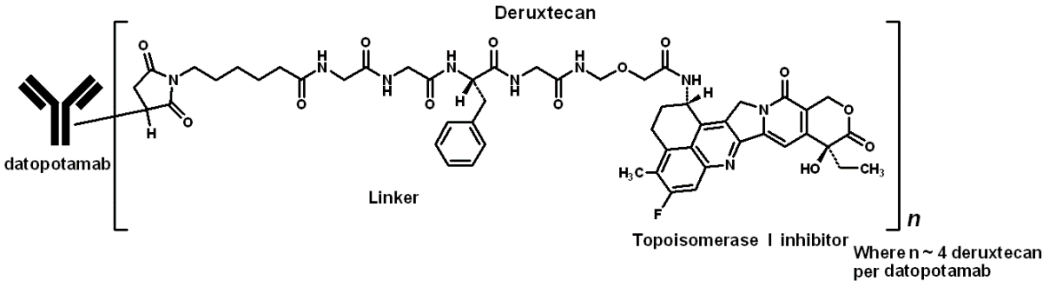
In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Datopotamab deruxtecan is an antibody-drug conjugate (ADC) composed of three components: 1) a humanised anti-TROP2 IgG1 monoclonal antibody (mAb), covalently linked to 2) a topoisomerase I inhibitor, an exatecan derivative, via 3) a tetrapeptide based cleavable linker. Deruxtecan is composed of the linker and the topoisomerase I inhibitor.

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

Figure 3. General structure of datopotamab deruxtecan



CAS number

2238831-60-0

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription only medicine (Schedule 4).

8 SPONSOR

AstraZeneca Pty Ltd
ABN 54 009 682 311
66 Talavera Road
MACQUARIE PARK NSW 2113

Telephone: 1800 805 342

9 DATE OF FIRST APPROVAL

To be confirmed.

10 DATE OF REVISION

Not applicable.

VV-RIM-04953501 V2.1