CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761394Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	BLA
Application Number	761394
PDUFA Goal Date	January 29, 2025
Nexus TTT #	2024-8095, 2024-8097
Reviewer Name(s)	Brad Moriyama, Pharm.D., BCCCP
Team Leader	Naomi Boston, Pharm.D.
Deputy Division Director	Laura Zendel, Pharm.D.
Review Completion Date	January 13, 2025
Subject	Evaluation of Need for a REMS
Established Name	datopotamab deruxtecan-dlnk
Trade Name	Datroway
Name of Applicant	Daiichi Sankyo, Inc.
Therapeutic Class	Trop-2-directed antibody and topoisomerase inhibitor conjugate
Formulation(s)	100 mg vial
Dosing Regimen	datopotamab deruxtecan-dlnk 6 mg/kg intravenous infusion once every 3 weeks (21-day cycle)

Table of Contents

EXECUTIVE SUMMARY 3

1. Introduction 3

2. Background 4

2.1. Product Information 4

2.2. Regulatory History 4

3. Therapeutic Context and Treatment Options 4

3.1. Description of the Medical Condition 4

3.2. Description of Current Treatment Options 5

4. Benefit Assessment 6

5. Risk Assessment & Safe-Use Conditions 6

5.1. Interstitial Lung Disease/Pneumonitis 7

5.2. Ocular Adverse Reactions 8

5.3. Stomatitis 8

5.4. Embryo-Fetal Toxicity 9

6. Expected Postmarket Use 9

7. Risk Management Activities Proposed by the Applicant 9

8. Discussion of Need for a REMS 9

9. Conclusion & Recommendations 10

10. Appendices 10

10.1. References 10

EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Datroway (datopotamab deruxtecan-dlnk) is necessary to ensure the benefits outweigh its risks. Daiichi Sankyo, Inc. submitted a Biologic Licensing Application (BLA) 761394 for datopotamab deruxtecan-dlnk with the proposed indication 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 (b) (4) for unresectable or metastatic disease. The FDA approved indication will be for the treatment of adult patients with unresectable or metastatic, HR-positive, 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. The serious risks associated with datopotamab deruxtecan-dlnk include interstitial lung disease/pneumonitis, ocular adverse reactions, stomatitis, and embryo-fetal toxicity. The applicant did not submit a proposed REMS or risk management plan with this application.

DRM and Division of Oncology 1 (D01) agree that a REMS is not necessary to ensure the benefits of datopotamab deruxtecan-dlnk outweigh its risks. The efficacy of datopotamab deruxtecan-dlnk was supported by the TROPION-Breast01 study, in which the datopotamab deruxtecan-dlnk group had a median progression-free survival of 6.9 months. The serious risks associated with datopotamab deruxtecan-dlnk of interstitial lung disease/pneumonitis, ocular adverse reactions, stomatitis, and embryo-fetal toxicity will be communicated in the warnings and precautions section of the label. The likely prescribers will be oncologists who should have experience managing the serious adverse events reported with datopotamab deruxtecan-dlnk.

1. Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME)[a] Datroway (datopotamab deruxtecan-dlnk) is necessary to ensure the benefits outweigh its risks. Daiichi Sankyo, Inc. submitted a Biologic Licensing Application (BLA) 761394 for datopotamab deruxtecan-dlnk with the proposed indication 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 (b) (4) for unresectable or metastatic disease.[1] This application is under review in the Division of Oncology 1 (DO1). The applicant did not submit a proposed REMS or risk management plan.

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

2. Background

2.1. Product Information

Datroway (datopotamab deruxtecan-dlnk), a NME, is a Trop-2-directed antibody and topoisomerase inhibitor conjugate, proposed for the treatment of adult patients with unresectable or metastatic HR-positive, HER2-negative (IHC 0, IHC 1+ or IHC 2+/ISH-) breast cancer who have received prior (b) (4) (b) (4) for unresectable or metastatic disease. Datopotamab deruxtecan-dlnk is a humanized anti-Trop2 IgG1 monoclonal antibody covalently linked to a topoisomerase 1 inhibitor (DXd) via a tetrapeptide-based cleavable linker. Following binding to Trop2 on cells, including tumor cells, datopotamab deruxtecan-dlnk undergoes internalization and intracellular linker cleavage by lysosomal enzymes. Upon release, the membrane-permeable DXd causes DNA damage and apoptotic cell death. Datopotamab deruxtecan-dlnk is proposed to be supplied as a 100 mg lyophilized powder in a single-dose vial. The proposed dosing regimen is datopotamab deruxtecan-dlnk 6 mg/kg (up to a maximum of 540 mg for patients ≥ 90 kg) intravenous infusion once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity.[b] Datopotamab deruxtecan-dlnk was first approved outside of the United States in Japan in 2024.

2.2. Regulatory History

The following is a summary of the regulatory history for datopotamab deruxtecan-dlnk BLA 761394 relevant to this review:

- 01/29/2024: BLA 761394 submission for the treatment of adult patients with unresectable or metastatic HR-positive, HER2-negative (IHC 0, IHC 1+ or IHC 2+/ISH-) breast cancer who have received prior (b) (4) for unresectable or metastatic disease received
- 10/28/2024: A Post Late-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for datopotamab deruxtecan-dlnk.

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

Breast cancer is a common cause of cancer in women in the United States.[2] The estimated number of new cases of breast cancer in the United States in women and in men is 310,720 and 2790,

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

respectively.[3,c] Histopathological subtypes of breast cancer are defined by expression of the estrogen receptor (ER), progesterone receptor (PR), and/or HER2.[4,5] Approximately 70% of patients with breast cancer will have HR-positive, HER2-negative disease. Furthermore, the estimated number of women with metastatic breast cancer in the United States in 2017 was 154,794.[6] Metastatic breast cancer is currently not curable and the five year relative survival of distant breast cancer is 31.9%.[2,7,d]

3.2. Description of Current Treatment Options

The treatment of recurrent or stage IV breast cancer increases survival and quality of life.[2] Current guidelines from the National Comprehensive Cancer Network (NCCN) for Breast Cancer list an aromatase inhibitor + CDK4/6 inhibitor and fulvestrant + CDK4/6 inhibitor as first line therapy in the "Preferred Regimens" section for systemic therapy for ER - and/or PR-positive HER2-negative recurrent unresectable or stage IV disease. For patients who have exhausted or are not suitable for endocrine therapy, single-agent chemotherapy is the standard of care.[5] For patients with HR-positive and HER2-negative endocrine refractory disease with no germline *BRCA* 1/2 mutation, the NCCN guidelines recommend systemic chemotherapy as first line treatment including anthracyclines, taxanes, capecitabine, gemcitabine, vinorelbine, or eribulin.

Recently, the antibody-drug conjugates Enhertu (fam-trastuzumab deruxtecan-nxki) and Trodelvy (sacituzumab govitecan-hziy) have been approved for the treatment of breast cancer.[5] Fam-trastuzumab deruxtecan-nxki, a HER2-directed antibody and topoisomerase inhibitor conjugate, was approved by the FDA for indications including adult patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer, as determined by an FDA-approved test, who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy.[8] Labeling includes a boxed warning for interstitial lung disease (ILD) and embryo-fetal toxicity. The other serious risks associated with fam-trastuzumab deruxtecan-nxki in the warnings and precautions section of the label include neutropenia and left ventricular dysfunction. Fam-trastuzumab deruxtecan-nxki was approved in 2019. Sacituzumab govitecan-hziy, a Trop-2-directed antibody and topoisomerase inhibitor conjugate, was approved by the FDA for indications including treatment of adult patients with unresectable locally advanced or metastatic HR-positive, HER2-negative (IHC 0, IHC 1+ or IHC 2+/ISH–) breast cancer who have received endocrine-based therapy and at least two additional systemic therapies in the metastatic setting.[9] Labeling includes a boxed warning for neutropenia and diarrhea. The other serious risks associated with sacituzumab govitecan-hziy in the warnings and precautions section of the label include hypersensitivity and infusion-related reactions, nausea and vomiting, increased risk of adverse reactions in patients with

[c] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

[d] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

reduced UGT1A1 activity, and embryo-fetal toxicity. Sacituzumab govitecan-hziy was approved in 2020. Fam-trastuzumab deruxtecan-nxki and sacituzumab govitecan-hziy did not require a REMS for approval.

Please refer to the DO1 multi-disciplinary review and evaluation for datopotamab deruxtecan-dlnk for a detailed clinical review on treatment armamentarium relevant to the proposed indication.

4. Benefit Assessment

The pivotal trial TROPION-Breast01 (NCT 05104866) supporting this application for efficacy and safety consisted of a Phase 3, multicenter, open-label, randomized study which evaluated datopotamab deruxtecan-dlnk in patients with unresectable or metastatic HR-positive, HER2-negative (IHC 0, IHC1+ or IHC2+/ISH-) breast cancer.[1,5] Eligible patients must have progressed on and deemed not suitable for further endocrine therapy and were required to have received 1 or 2 lines of prior chemotherapy in the unresectable or metastatic disease setting. Patients (N=732) were randomized to datopotamab deruxtecan-dlnk 6 mg/kg by intravenous infusion every 3 weeks (N=365) or investigator's choice of chemotherapy (N=367) until unacceptable toxicity or disease progression. Investigator's choice of chemotherapy included eribulin, capecitabine, vinorelbine, or gemcitabine. The primary endpoints 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). The median PFS was 6.9 months in the datopotamab deruxtecan-dlnk group (95% CI 5.7 to 7.4) and 4.9 months in the chemotherapy group (95% CI 4.2 to 5.5), hazard ratio 0.63 (95% CI 0.52 to 0.76), $p < 0.0001$. The median OS was 18.6 months in the datopotamab deruxtecan-dlnk group and 18.3 months in the chemotherapy group, hazard ratio 1.01 (95% CI 0.83 to 1.22), p = not significant.

Secondary endpoints included confirmed objective response rate (ORR) and duration of response (DOR) by BICR. The ORR was 36% in the datopotamab deruxtecan-dlnk group (95% CI 31 to 42) and 23% in the chemotherapy group (95% CI 19 to 28). The median DOR was 6.7 months in the datopotamab deruxtecan-dlnk group (95% CI 5.6 to 9.8) and 5.7 months in the chemotherapy group (95% CI 4.9 to 6.8). The clinical reviewer concluded datopotamab deruxtecan-dlnk was associated with a statistically significant improvement in PFS and an OS HR~1 indicating no potential detriment but also no improvement.[e]

5. Risk Assessment & Safe-Use Conditions

[e] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

The safety of datopotamab deruxtecan-dlnk was evaluated in a Phase 3 clinical trial TROPION-Breast01.[1,5,f] In the safety population, 360 patients received datopotamab deruxtecan-dlnk and 351 patients received investigator's choice of chemotherapy. Discontinuation due to an adverse reaction occurred in 3.1% in the datopotamab deruxtecan-dlnk group and 2.8% in the chemotherapy group. Common adverse reactions including laboratory abnormalities reported with datopotamab deruxtecan-dlnk were stomatitis, nausea, fatigue, decreased leukocytes, decreased calcium, alopecia, decreased lymphocytes, decreased hemoglobin, constipation, decreased neutrophils, dry eye, vomiting, increased alanine aminotransferase (ALT), keratitis, increased aspartate aminotransferase (AST), and increased alkaline phosphatase.

In study TROPION-Breast01, there were 2 deaths due to an adverse event in the datopotamab deruxtecan-dlnk group and 4 deaths were due to an adverse event in the chemotherapy group.[5] In the datopotamab deruxtecan-dlnk group, 1 death was due to sepsis and 1 death was due to ILD/pneumonitis. Per the clinical reviewer's assessment of the deaths, the cause of death due to ILD/pneumonitis was related to datopotamab deruxtecan-dlnk and the cause of death due to sepsis was unlikely related to datopotamab deruxtecan-dlnk.

The serious risks[g] associated with datopotamab deruxtecan-dlnk which include interstitial lung disease/pneumonitis, ocular adverse reactions, stomatitis, and embryo-fetal toxicity are summarized in the sections below.

5.1. Interstitial Lung Disease/Pneumonitis

Datopotamab deruxtecan-dlnk can cause severe, life-threatening, or fatal ILD or pneumonitis. An adverse reaction of ILD/pneumonitis occurred in 4.2% of patients receiving datopotamab deruxtecan-dlnk, with Grade 3-4 ILD/pneumonitis reported in 0.5% of patients and fatal ILD/pneumonitis reported in 0.3% of patients. The proposed label recommends to monitor patients for new or worsening respiratory symptoms indicative of ILD/pneumonitis (e.g., dyspnea, cough, fever) during treatment with datopotamab deruxtecan-dlnk. It states for asymptomatic (Grade 1) ILD/pneumonitis, consider corticosteroid treatment (e.g. ≥ 0.5 mg/kg/day prednisolone or equivalent). It recommends for symptomatic ILD/pneumonitis (Grade 2 or greater), promptly initiate systemic corticosteroid treatment

[f] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug*

[g] Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

(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. It also recommends to withhold datopotamab deruxtecan-dlnk in patients with suspected ILD/pneumonitis and permanently discontinue datopotamab deruxtecan-dlnk if ≥ Grade 2 ILD/pneumonitis is confirmed. If approved, this risk will be communicated in the warnings and precautions section of the label.

5.2. Ocular Adverse Reactions

Datopotamab deruxtecan-dlnk can cause ocular adverse reactions, including dry eye, keratitis, blepharitis, meibomian gland dysfunction, increased lacrimation, conjunctivitis, and blurred vision. An adverse reaction of ocular adverse reactions occurred in 51% of patients receiving datopotamab deruxtecan-dlnk, with Grade 3 ocular adverse reactions including dry eye, keratitis, and blurred vision reported in 1.9% of patients. Ocular adverse reactions occurred with a median time to onset of 2.1 months, with a range from 0.03 months to 23.2 months; 45% of patients had complete resolution and 9% had partial improvement (defined as a decrease in severity by one or more grades from the worst grade at last follow up).

The proposed label states to advise patients to use preservative-free lubricant eye drops several times daily for prophylaxis and to advise patients to avoid use of contact lenses unless directed by an eye care professional. The proposed label recommends to 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. It recommends to promptly refer patients to an eye care professional for any new or worsening ocular adverse reactions, to monitor patients for ocular adverse reactions during treatment with datopotamab deruxtecan-dlnk, and if diagnosis is confirmed, dose delay, dose reduce, or permanently discontinue datopotamab deruxtecan-dlnk based on severity. If approved, this risk will be communicated in the warnings and precautions section of the label.

5.3. Stomatitis

Datopotamab deruxtecan-dlnk can cause stomatitis, including mouth ulcers and oral mucositis. An adverse reaction of stomatitis occurred in 59% of patients receiving datopotamab deruxtecan-dlnk, with Grade 3-4 stomatitis reported in 7% of patients. The proposed label states to advise patients to use a steroid-containing mouthwash for prophylaxis and treatment of stomatitis. The proposed label recommends to instruct the patient to hold ice chips or ice water in the mouth throughout the infusion of datopotamab deruxtecan-dlnk. It recommends to monitor patients for signs and symptoms of stomatitis, if stomatitis occurs increase the frequency of mouthwash and administer other topical treatments as clinically indicated, and based on the severity of the adverse reaction, withhold, dose reduce, or permanently discontinue datopotamab deruxtecan-dlnk. If approved, this risk will be communicated in the warnings and precautions section of the label.

5.4. Embryo-Fetal Toxicity

Datopotamab deruxtecan-dlnk can cause embryo-fetal harm based on the mechanism of action of the drug. No clinical data is available with datopotamab deruxtecan-dlnk in pregnancy in humans. The topoisomerase inhibitor component of datopotamab deruxtecan-dlnk, DXd, is genotoxic and affects actively dividing cells. The risk of embryo-fetal toxicity is proposed to be included in a Medication Guide and the warnings and precautions section of the label. The proposed label states advise patients of the potential risk to a fetus. The proposed label recommends in females of reproductive potential to verify pregnancy status before starting datopotamab deruxtecan-dlnk and that effective contraception be used during treatment and for 7 months after the last dose. In addition, in males with a female partner of reproductive potential it is recommended that effective contraception be used during treatment and for 4 months after the last dose.

6. Expected Postmarket Use

If approved, datopotamab deruxtecan-dlnk will primarily be used in both inpatient and outpatient (such as infusion centers) settings. The likely prescribers will be oncologists.

7. Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for datopotamab deruxtecan-dlnk beyond routine pharmacovigilance and labeling.

8. Discussion of Need for a REMS

The clinical reviewer recommends approval of datopotamab deruxtecan-dlnk on the basis of the efficacy and safety information currently available. If approved, datopotamab deruxtecan-dlnk will be another treatment option for patients with unresectable or metastatic HR+/HER2- breast cancer.[5] The efficacy of datopotamab deruxtecan-dlnk was supported by study TROPION-Breast01, in which the datopotamab deruxtecan-dlnk group had a median PFS of 6.9 months. The serious risks associated with datopotamab deruxtecan-dlnk of ILD/pneumonitis, ocular adverse reactions, stomatitis, and embryo-fetal toxicity will be communicated in the warnings and precautions section of the label. None of the risks associated with datopotamab deruxtecan-dlnk rise to the level of a boxed warning. The clinical reviewer stated datopotamab deruxtecan-dlnk demonstrated acceptable safety in the indicated population with a serious and life-threatening disease and the safety profile is manageable through labeling.

Breast cancer is a common cause of cancer in women in the United States. The estimated number of new cases of breast cancer in the United States in women and in men is 310,720 and 2790, respectively. Approximately 70% of patients with breast cancer will have HR-positive, HER2-negative disease. Furthermore, the estimated number of women with metastatic breast cancer in the United States in

2017 was 154,794. Metastatic breast cancer is currently not curable and the five year relative survival of distant breast cancer is 31.9%. The likely prescribers will be oncologists who are expected to have experience managing the serious adverse events reported with datopotamab deruxtecan-dlnk. If approved, based on the efficacy and risks associated with datopotamab deruxtecan-dlnk for the treatment of adult patients with unresectable or metastatic, HR-positive, 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, the DRM and D01 agree that a REMS is not necessary to ensure that the benefits outweigh the risks as the risk can be adequately communicated in labeling.

9. Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable therefore, a REMS is not necessary for datopotamab deruxtecan-dlnk to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10. Appendices

10.1. References

[1] Proposed prescribing information for datopotamab deruxtecan-dlnk as currently edited by FDA, last accessed January 3, 2025.

[2] National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology (NCCN Guidelines®). Breast cancer (version 6.2024 – November 11, 2024). https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf (accessed 2024 December 13).

[3] Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024. *CA Cancer J Clin*. 2024;74(1):12-49.

[4] Howlader N, Altekruse SF, Li CI, et al. US incidence of breast cancer subtypes defined by joint hormone receptor and HER2 status. *J Natl Cancer Inst*. 2014;106(5).

[5] Datroway (datopotamab deruxtecan-dlnk) BLA 761394 multi-disciplinary review and evaluation. Last accessed January 3, 2025.

[6] Mariotto AB, Etzioni R, Hurlbert M, Penberthy L, Mayer M. Estimation of the Number of Women Living with Metastatic Breast Cancer in the United States. Cancer Epidemiol Biomarkers Prev. 2017;26(6):809-815.

[7] Cancer Stat Facts: Female Breast Cancer. National Cancer Institute Surveillance, Epidemiology, and End Results Program. https://seer.cancer.gov/statfacts/html/breast.html (accessed 2024 December 30)

[8] Enhertu (fam-trastuzumab deruxtecan-nxki) package insert. Basking Ridge, NJ: Daiichi Sankyo, Inc.; 2024 April.

[9] Trodelvy (sacituzumab govitecan-hziy) package insert. Foster City, CA: Gilead Sciences, Inc.; 2024 November.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

BRAD T MORIYAMA
01/13/2025 03:53:17 PM

NAOMI S BOSTON
01/13/2025 04:23:29 PM

LAURA A ZENDEL
01/13/2025 04:25:36 PM