2021 FALL CLINICAL VIRTUAL MEETING

OCTOBER 22, 2021

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MorphoSys Company Overview

Founded in Germany in 1992, MorphoSys is now one of the world's leading biotechnology companies with expertise in antibody, protein, and peptide engineering

We are headquartered near Munich, Germany and in Boston, MA

MONJUVI (tafasitamab-cxix) – Our key asset launched in the U.S. for the treatment of adult patients with relapsed or refractory DLBCL not eligible for AST in combination with Lenalidomide; in partnership with Incyte Corporation and approved under accelerated approval contingent upon a confirmatory trial(s)

We have >600 employees coming from 40 different nations and contributed to development of over 100 product candidates

MorphoSys announced the acquisition of Constellation Pharmaceuticals and a strategic funding partnership with Royalty Pharma in June 2021

Sources: https://www.morphosys.com/company/history; https://www.morphosys-us.com/our-mission; https://www.morphosys.com/pipeline/proprietary-portfolio/tafasitamab-mor208; https://morphosys-constellation-royaltypharma.com/;

Accelerating Our Innovation and Growth Strategy

Mid- to late-stage pipeline

ASSET	PARTNER	TARGET	DISEASE AREA	PHASE 1	PHASE 2	PHASE 3	MARKET
Monjuvi® (tafasitamab-cxix)[1]	Incyte	CD19	• r/r DLBCL* (L-MIND) • R/R DLBCL (B-MIND) • 1L DLBCL (frontMIND) • 1L DLBCL (firstMIND) • R/R FL / MZL (inMIND) • R/R CLL/SLL (COSMOS)				MONJUVI® tafasitamab-cxix | 200mg for injection, for intravenous use
Pelabresib[1]		BET	• Myelofibrosis (MANIFEST-2)				
Felzartamab[1]		CD38	• MN (New-PLACE) • MN (M-PLACE)				
CPI – 0209[1]		EZH2	• Solid tumors / Hematological malignancies				
Plamotamab[2]	Xencor, Incyte	CD20 & CD3	• R/R DLBCL • DLBCL, R/R FL				

*Monjuvi® (tafasitamab-cxix) is approved under accelerated approval by the U.S. FDA in combination with lenalidomide for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) not otherwise specified, including DLBCL arising from low grade lymphoma, and who are not eligible for autologous stem cell transplant (ASCT); r/r DLBCL: relapsed/refractory diffuse large B-cell lymphoma. r/r FL / MZL: relapsed/refractory Follicular Lymphoma or Marginal Zone Lymphoma; MN: membranous nephropathy; IgAN: IgA nephropathy)

1. https://www.morphosys.com/pipeline; accessed Sept. 20, 2021
2. https://www.morphosys.com/media-investors/media-center/xencor-morphosys-and-incyte-enter-into-global-development-collaboration; accessed Dec 21, 2020

Pipeline products are under clinical investigation and have not been proven to be safe or effective.

L-MIND: Baseline Characteristics

Characteristic	Specification	N=81
Age, years[a]	Median (range)	72 (41-86)
Sex, n (%)	Male	44 (54)
	Female	37 (46)
Ann Arbor stage, n (%)[a]	I-II	20 (25)
	III-IV	61 (75)
Risk (IPI), n (%)[a]	0-2	40 (49)
	3-5	41 (51)
Elevated LDH, n (%)[a]	Yes	45 (56)
	No	36 (44)
Prior lines, n (%)[a]	Median	2
	1	40 (49)
	2	35 (43)
	3	5 (6)
	4	1 (1)

Characteristic	Specification	N=81
Primary refractory, n (%)[a]	Yes	15 (19)[b]
	No	66 (81)
Refractory to previous therapy line, n (%)[a]	Yes	36 (44)
	No	45 (56)
Prior SCT, n (%)	Yes	9 (11)
	No	72 (89)
Cell of origin (by IHC), n (%) (Centrally assessed—Hans algorithm)	GCB	37 (46)
	Non-GCB	20 (25)
	Unknown	24 (30)

[a]At study entry.
[b]Primary refractory patients had a DoR to 1L of 3-6 months.
GCB = germinal center B-cell–like; IHC = immunohistochemistry; IPI = International Prognostic Index; LDH = lactate dehydrogenase; SCT = stem cell transplant.
Salles et al. *Lancet Oncol.* 2020;21:978.

L-MIND: Activity of Tafasitamab-cxix + LEN* Remained Durable After ≥35 Months in the FAS (N=80) Population

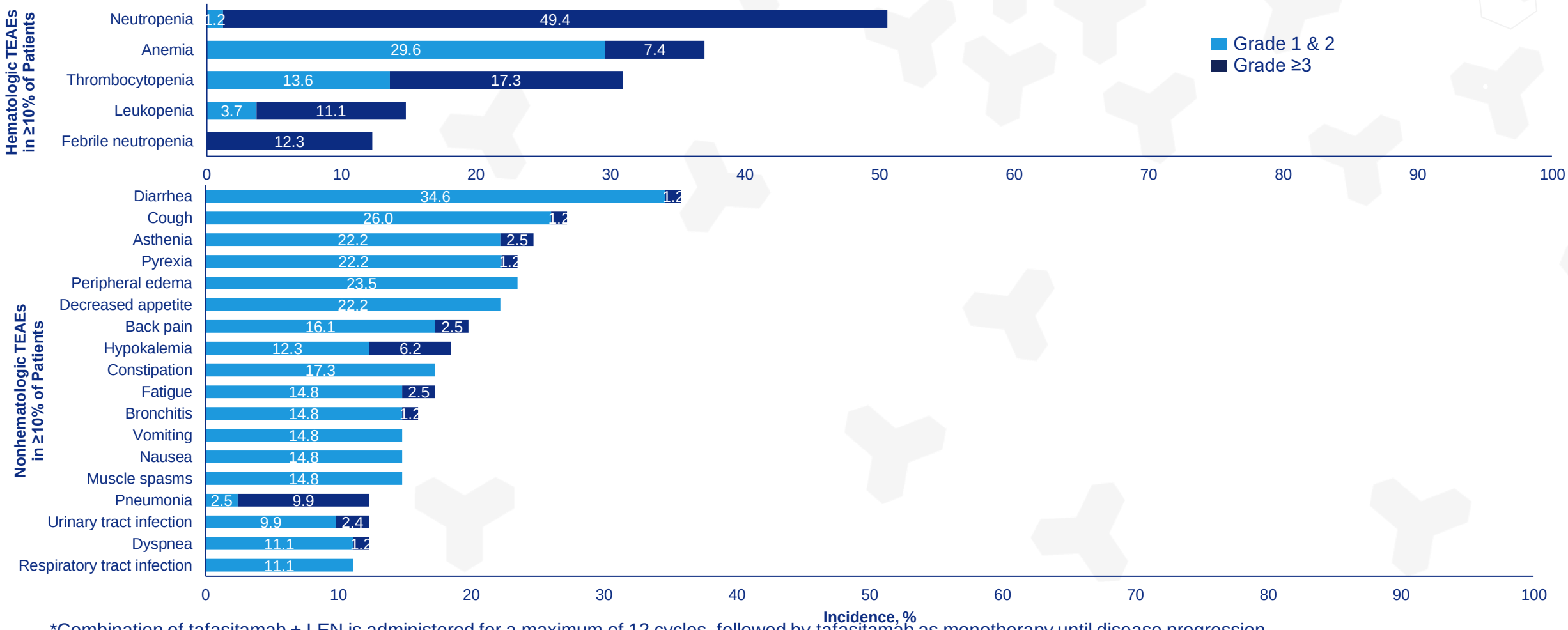
*Combination of Tafasitamab +LEN is administered for a maximum of 12 cycles, followed by Tafasitamab as monotherapy until disease progression or unacceptable toxicity

	12-Month Analysis[a]	24-Month Analysis[b]	35-Month Analysis[c]
	N=80 (FAS)[1]	N=80 (FAS)[2]	N=80 (FAS)[3]
ORR, %	60	57.5	57.5
CR, %	42.5	40.0	40.0
PR, %	17.5	17.5	17.5
mDoR (95% CI), months	21.7 (21.7-NR)	34.6 (26.1-NR)	43.9 (26.1-NR)
mPFS (95% CI), months	12.1 (5.7-NR)	12.1 (6.3-NR)	11.6 (6.3-45.7)
mOS (95% CI), months	NR (18.3-NR)	31.6(18.3-NR)	33.5 (18.3-NR)

The USPI includes efficacy data on a subset of patients with centrally confirmed diagnoses of DLBCL[4]: N=71; ORR=55%; mDoR=21.7 months after 12-month analysis

[a]Data cutoff: November 30, 2018.
[b]Data cutoff: November 30, 2019.
[c]Data cutoff: October 30, 2020.
FAS = full analysis set; mDoR = median DoR; mOS = median OS; mPFS = median PFS; NR = not reached.
1. Salles et al. *Lancet Oncol.* 2020;21:978; 2. Data on file, MOR208C203 EMA Analysis Tables_21Oct2020, MorphoSys US Inc.; 3. Data on file, IA_MOR208C203_Toplines_Tables_08JAN2021, MorphoSys US Inc.; 4. MONJUVI (tafasitamab-cxix) Prescribing Information.

Long-term Safety Profile* After ≥35 Months of Follow-up (IRC) With N=81 Patients



*Combination of tafasitamab + LEN is administered for a maximum of 12 cycles, followed by tafasitamab as monotherapy until disease progression or unacceptable toxicity.

TEAEs = treatment-emergent adverse events.

Duell et al._*Haematologica* 2021;106(9):2417-2426

MONJUVI®
tafasitamab-cxix | 200mg
for injection, for intravenous use

ANNOUNCING A **UNIQUE J-CODE** FOR MONJUVI:

J9349:

Injection, tafasitamab-cxix, 2mg
EFFECTIVE **APRIL 1, 2021**

USING J9349 MAY HELP WITH MORE TIMELY REIMBURSEMENT	
HCPCS Code	J9349
Effective Date	April 1, 2021
J-Code Descriptor	Injection, tafasitamab-cxix, 2mg
Single-Dose Vial Size	200mg
Billing Unit Conversion	One 200mg Single-Dose Vial = 100 Units

If date of service occurred before April 1, 2021, check with payers to determine appropriate coding.

My MISSION SUPPORT Patient Support Program™

For Billing and Coding or Reimbursement Questions, or to Request Support From a Member of the Field Access and Reimbursement Team, Call 855-421-6172, M-F 8 AM to 8 PM ET

The information herein is provided for educational purposes only. MorphoSys and Incyte cannot guarantee insurance coverage or reimbursement. Coverage and reimbursement may vary significantly by payer, plan, patient, and setting of care. It is the sole responsibility of the healthcare provider to select the proper codes and ensure the accuracy of all statements used in seeking coverage and reimbursement for an individual patient.

HCPCS – Healthcare Common Procedure Coding System.

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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use MONJUVI safely and effectively. See full prescribing information for MONJUVI.

MONJUVI® (tafasitamab-cxix) for injection, for intravenous use Initial U.S. Approval: 2020

---------- INDICATIONS AND USAGE ----------

MONJUVI is a CD19-directed cytolytic antibody indicated in combination with lenalidomide for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) not otherwise specified, including DLBCL arising from low grade lymphoma, and who are not eligible for autologous stem cell transplant (ASCT).

This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s). (1)

---------- DOSAGE AND ADMINISTRATION ----------

- Administer premedications prior to starting MONJUVI. (2.2)
- The recommended dosage of MONJUVI is 12 mg/kg as an intravenous infusion according to the following dosing schedule: (2.1)
  - Cycle 1: Days 1, 4, 8, 15 and 22 of the 28-day cycle.
  - Cycles 2 and 3: Days 1, 8, 15 and 22 of each 28-day cycle.
  - Cycle 4 and beyond: Days 1 and 15 of each 28-day cycle.
- Administer MONJUVI in combination with lenalidomide for a maximum of 12 cycles and then continue MONJUVI as monotherapy until disease progression or unacceptable toxicity. (2.1)
- See Full Prescribing Information for instructions on preparation and administration. (2.3, 2.4)

---------- DOSAGE FORMS AND STRENGTHS ----------

For injection: 200 mg of tafasitamab-cxix as lyophilized powder in single-dose vial for reconstitution. (3)

---------- CONTRAINDICATIONS ----------

None.

---------- WARNINGS AND PRECAUTIONS ----------

- Infusion-Related Reactions: Monitor patients frequently during infusion. Interrupt or discontinue infusion based on severity. (2.3, 5.1)
- Myelosuppression: Monitor complete blood counts. Manage using dose modifications and growth factor support. Interrupt or discontinue MONJUVI based on severity. (2.3, 5.2)
- Infections: Bacterial, fungal and viral infections can occur during and following MONJUVI. Monitor patients for infections. (2.3, 5.3)
- Embryo-Fetal Toxicity: May cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and use of effective contraception. (5.4)

---------- ADVERSE REACTIONS ----------

The most common adverse reactions (≥20%) are neutropenia, fatigue, anemia, diarrhea, thrombocytopenia, cough, pyrexia, peripheral edema, respiratory tract infection, and decreased appetite. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact MORPHOSYS US INC. at 1-844-667-1992 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- USE IN SPECIFIC POPULATIONS ----------

Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 6/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

MONJUVI, in combination with lenalidomide, is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) not otherwise specified, including DLBCL arising from low grade lymphoma, and who are not eligible for autologous stem cell transplant (ASCT).

This indication is approved under accelerated approval based on overall response rate *[see Clinical Studies (14)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dose of MONJUVI is 12 mg/kg based on actual body weight administered as an intravenous infusion according to the dosing schedule in Table 1.

Administer MONJUVI in combination with lenalidomide 25 mg for a maximum of 12 cycles, then continue MONJUVI as monotherapy until disease progression or unacceptable toxicity *[see Clinical Studies (14)]*. Refer to the lenalidomide prescribing information for lenalidomide dosage recommendations.

TABLE 1: MONJUVI Dosing Schedule

Cycle*	Dosing schedule
Cycle 1	Days 1, 4, 8, 15 and 22
Cycles 2 and 3	Days 1, 8, 15 and 22
Cycle 4 and beyond	Days 1 and 15

*Each treatment cycle is 28-days.

MONJUVI should be administered by a healthcare professional with immediate access to emergency equipment and appropriate medical support to manage infusion-related reactions (IRRs) *[see Warnings and Precautions (5.1)]*.

2.2 Recommended Premedications

Administer premedications 30 minutes to 2 hours prior to starting MONJUVI infusion to minimize infusion-related reactions *[see Warnings and Precautions (5.1)]*. Premedications may include acetaminophen, histamine H_1 receptor antagonists, histamine H_2 receptor antagonists, and/or glucocorticosteroids.

For patients not experiencing infusion-related reactions during the first 3 infusions, premedication is optional for subsequent infusions.

If a patient experiences an infusion-related reaction, administer premedications before each subsequent infusion.

2.3 Dosage Modifications for Adverse Reactions

The recommended dosage modifications for adverse reactions are summarized in Table 2.

TABLE 2: Dosage Modifications for Adverse Reactions

Adverse Reaction	Severity	Dosage Modification
Infusion-related reactions *[see Warnings and Precautions (5.1)]*	Grade 2 (moderate)	• Interrupt infusion immediately and manage signs and symptoms. • Once signs and symptoms resolve or reduce to Grade 1, resume infusion at no more than 50% of the rate at which the reaction occurred. If the patient does not experience further reaction within 1 hour and vital signs are stable, the infusion rate may be increased every 30 minutes as tolerated to the rate at which the reaction occurred.
	Grade 3 (severe)	• Interrupt infusion immediately and manage signs and symptoms. • Once signs and symptoms resolve or reduce to Grade 1, resume infusion at no more than 25% of the rate at which the reaction occurred. If the patient does not experience further reaction within 1 hour and vital signs are stable, the infusion rate may be increased every 30 minutes as tolerated to a maximum of 50% of the rate at which the reaction occurred. • If after rechallenge the reaction returns, stop the infusion immediately.
	Grade 4 (life-threatening)	• Stop the infusion immediately and permanently discontinue MONJUVI.
Myelosuppression *[see Warnings and Precautions (5.2)]*	Platelet count of 50,000/mcL or less	• Withhold MONJUVI and lenalidomide and monitor complete blood count (CBC) weekly until platelet count is 50,000/mcL or higher. • Resume MONJUVI at the same dose and lenalidomide at a reduced dose. Refer to lenalidomide prescribing information for dosage modifications.
	Neutrophil count of 1,000/mcL or less for at least 7 days OR Neutrophil count of 1,000/mcL or less with an increase of body temperature to 100.4°F (38°C) or higher OR Neutrophil count less than 500/mcL	• Withhold MONJUVI and lenalidomide and monitor CBC weekly until neutrophil count is 1,000/mcL or higher. • Resume MONJUVI at the same dose and lenalidomide at a reduced dose. Refer to lenalidomide prescribing information for dosage modifications.

2.4 Preparation and Administration

Reconstitute and dilute MONJUVI prior to infusion.

Reconstitution

1. Calculate the dose (mg) and determine the number of vials needed.
2. Reconstitute each 200 mg MONJUVI vial with 5 mL Sterile Water for Injection, USP with the stream directed toward the wall of each vial to obtain a final concentration of 40 mg/mL tafasitamab-cxix.
3. Gently swirl the vial(s) until completely dissolved. Do not shake or swirl vigorously. Complete dissolution may take up to 5 minutes.
4. Visually inspect the reconstituted solution for particulate matter or discoloration. The reconstituted solution should appear as a colorless to slightly yellow solution. Discard the vial(s) if the solution is cloudy, discolored, or contains visible particles.
5. Use the reconstituted MONJUVI solution immediately. If needed, store the reconstituted solution in the vial for a maximum of 12 hours either refrigerated at 36°F to 46°F (2°C to 8°C) or room temperature at 68°F to 77°F (20°C to 25°C) before dilution. Protect from light during storage.

Dilution

1. Determine the volume (mL) of the 40 mg/mL reconstituted MONJUVI solution needed based on the required dose.
2. Remove a volume equal to the required MONJUVI solution from a 250 mL 0.9% Sodium Chloride Injection, USP infusion bag and discard it.
3. Withdraw the necessary amount of MONJUVI and slowly dilute in the infusion bag that contains the 0.9% Sodium Chloride Injection, USP to a final concentration of 2 mg/mL to 8 mg/mL. Discard any unused portion of MONJUVI remaining in the vial.
4. Gently mix the intravenous bag by slowly inverting the bag. *Do not shake*. Visually inspect the infusion bag with the diluted MONJUVI infusion solution for particulate matter and discoloration prior to administration.
5. If not used immediately, store the diluted MONJUVI infusion solution refrigerated for up to 18 hours at 36°F to 46°F (2°C to 8°C) and/or at room temperature for up to 12 hours at 68°F to 77°F (20°C to 25°C). The room temperature storage includes time for infusion. Protect from light during storage.

Do not shake or freeze the reconstituted or diluted infusion solutions.

Administration

- Administer MONJUVI as an intravenous infusion.
  - For the first infusion, use an infusion rate of 70 mL/h for the first 30 minutes, then, increase the rate so that the infusion is administered within 1.5 to 2.5 hours.
  - Administer all subsequent infusions within 1.5 to 2 hours.
- Infuse the entire contents of the bag containing MONJUVI.
- Do not co-administer other drugs through the same infusion line.
- No incompatibilities have been observed between MONJUVI with infusion containers made of polypropylene (PP), polyvinylchloride (PVC), polyethylene (PE), polyethylenterephthalate (PET), or glass and infusion sets made of polyurethane (PUR) or PVC.

3 DOSAGE FORMS AND STRENGTHS

For injection: 200 mg of tafasitamab-cxix as white to slightly yellowish lyophilized powder in single-dose vial for reconstitution and further dilution.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Infusion-Related Reactions

MONJUVI can cause infusion-related reactions *[see Adverse Reactions (6.1)]*. In L-MIND, infusion-related reactions occurred in 6% of the 81 patients. Eighty percent of infusion-related reactions occurred during cycle 1 or 2. Signs and symptoms included fever, chills, rash, flushing, dyspnea, and hypertension. These reactions were managed with temporary interruption of the infusion and/or with supportive medication.

Premedicate patients prior to starting MONJUVI infusion *[see Dosage and Administration (2.2)]*. Monitor patients frequently during infusion. Based on the severity of the infusion-related reaction, interrupt or discontinue MONJUVI *[see Dosage and Administration (2.3)]*. Institute appropriate medical management.

5.2 Myelosuppression

MONJUVI can cause serious or severe myelosuppression, including neutropenia, thrombocytopenia, and anemia *[see Adverse Reactions (6.1)]*. In L-MIND, Grade 3 neutropenia occurred in 25% of patients, thrombocytopenia in 12%, and anemia in 7%. Grade 4 neutropenia occurred in 25% and thrombocytopenia in 6%. Neutropenia led to treatment discontinuation in 3.7% of patients.

Monitor CBC prior to administration of each treatment cycle and throughout treatment. Monitor patients with neutropenia for signs of infection. Consider granulocyte colony-stimulating factor administration. Withhold MONJUVI based on the severity of the adverse reaction *[see Dosage and Administration (2.3)]*. Refer to the lenalidomide prescribing information for dosage modifications.

5.3 Infections

Fatal and serious infections, including opportunistic infections, occurred in patients during treatment with MONJUVI and following the last dose *[see Adverse Reactions (6.1)]*.

In L-MIND, 73% of the 81 patients developed an infection. The most frequent infections were respiratory tract infection (24%), urinary tract infection (17%), bronchitis (16%), nasopharyngitis (10%) and pneumonia (10%). Grade 3 or higher infection occurred in 30% of the 81 patients. The most frequent grade 3 or higher infection was pneumonia (7%). Infection-related deaths were reported in 2.5% of the 81 patients.

Monitor patients for signs and symptoms of infection and manage infections as appropriate.

5.4 Embryo-Fetal Toxicity

Based on its mechanism of action, MONJUVI may cause fetal B-cell depletion when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with MONJUVI and for at least 3 months after the last dose *[see Use in Specific Populations (8.1, 8.3)]*.

MONJUVI is initially administered in combination with lenalidomide. The combination of MONJUVI with lenalidomide is contraindicated in pregnant women because lenalidomide can cause birth defects and death of the unborn child. Refer to the lenalidomide prescribing information on use during pregnancy.

6 ADVERSE REACTIONS

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

- Infusion-related reactions *[see Warnings and Precautions (5.1)]*
- Myelosuppression *[see Warnings and Precautions (5.2)]*
- Infections *[see Warnings and Precautions (5.3)]*

6.1 Clinical Trials Experience

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

Relapsed or Refractory Diffuse Large B-Cell Lymphoma

The safety of MONJUVI was evaluated in L-MIND *[see Clinical Studies (14)]*. Patients (n=81) received MONJUVI 12 mg/kg intravenously in combination with lenalidomide for a maximum of 12 cycles, followed by MONJUVI as monotherapy until disease progression or unacceptable toxicity as follows:

- Cycle 1: Days 1, 4, 8, 15 and 22 of the 28-day cycle;
- Cycles 2 and 3: Days 1, 8, 15 and 22 of each 28-day cycle;
- Cycles 4 and beyond: Days 1 and 15 of each 28-day cycle.

Among patients who received MONJUVI, 57% were exposed for 6 months or longer, 42% were exposed for greater than one year, and 24% were exposed for greater than two years.

Serious adverse reactions occurred in 52% of patients who received MONJUVI. Serious adverse reactions in ≥6% of patients included infections (26%), including pneumonia (7%), and febrile neutropenia (6%). Fatal adverse reactions occurred in 5% of patients who received MONJUVI, including cerebrovascular accident (1.2%), respiratory failure (1.2%), progressive multifocal leukoencephalopathy (1.2%) and sudden death (1.2%).

Permanent discontinuation of MONJUVI or lenalidomide due to an adverse reaction occurred in 25% of patients and permanent discontinuation of MONJUVI due to an adverse reaction occurred in 15%. The most frequent adverse reactions which resulted in permanent discontinuation of MONJUVI were infections (5%), nervous system disorders (2.5%), respiratory, thoracic and mediastinal disorders (2.5%).

Dosage interruptions of MONJUVI or lenalidomide due to an adverse reaction occurred in 69% of patients and dosage interruption of MONJUVI due to an adverse reaction occurred in 65%. The most frequent adverse reactions which required a dosage interruption of MONJUVI were blood and lymphatic system disorders (41%), and infections (27%).

The most common adverse reactions (≥20%) were neutropenia, fatigue, anemia, diarrhea, thrombocytopenia, cough, pyrexia, peripheral edema, respiratory tract infection, and decreased appetite.

Table 3 summarizes the adverse reactions in L-MIND.

TABLE 3: Adverse Reactions (≥10%) in Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma Who Received MONJUVI in L-MIND

Adverse Reaction	MONJUVI (N=81)	
	All Grades (%)	Grade 3 or 4 (%)
Blood and lymphatic system disorders		
Neutropenia	51	49
Anemia	36	7
Thrombocytopenia	31	17
Febrile neutropenia	12	12
General disorders and administration site conditions		
Fatigue*	38	3.7
Pyrexia	24	1.2
Peripheral edema	24	0
Gastrointestinal disorders		
Diarrhea	36	1.2
Constipation	17	0
Abdominal pain^	15	1.2
Nausea	15	0
Vomiting	15	0
Respiratory, thoracic and mediastinal disorders		
Cough	26	1.2
Dyspnea	12	1.2
Infections		
Respiratory tract infection+	24	4.9
Urinary tract infection†	17	4.9
Bronchitis	16	1.2
Metabolism and nutrition disorders		
Decreased appetite	22	0
Hypokalemia	19	6
Musculoskeletal and connective tissue disorders		
Back pain	19	2.5
Muscle spasms	15	0
Skin and subcutaneous tissue disorders		
Rash‡	15	2.5
Pruritus	10	1.2

*Fatigue includes asthenia and fatigue

+Respiratory tract infection includes: lower respiratory tract infection, upper respiratory tract infection, respiratory tract infection

†Urinary tract infection includes: urinary tract infection, Escherichia urinary tract infection, urinary tract infection bacterial, urinary tract infection enterococcal

^Abdominal pain includes abdominal pain, abdominal pain lower, and abdominal pain upper

‡Rash includes rash, rash maculo-papular, rash pruritic, rash erythematous, rash pustular

Clinically relevant adverse reactions in <10% of patients who received MONJUVI were:

- *Blood and lymphatic system disorders:* lymphopenia (6%)
- *General disorders and administration site conditions:* infusion-related reaction (6%)
- *Infections:* sepsis (4.9%)
- *Investigations:* weight decreased (4.9%)
- *Musculoskeletal and connective tissue disorders:* arthralgia (9%), pain in extremity (9%), musculoskeletal pain (2.5%)
- *Neoplasms benign, malignant and unspecified:* basal cell carcinoma (1.2%)
- *Nervous system disorders:* headache (9%), paresthesia (7%), dysgeusia (6%)
- *Respiratory, thoracic and mediastinal disorders:* nasal congestion (4.9%), exacerbation of chronic obstructive pulmonary disease (1.2%)
- *Skin and subcutaneous tissue disorders:* erythema (4.9%), alopecia (2.5%), hyperhidrosis (2.5%)

Table 4 summarizes the laboratory abnormalities in L-MIND.

TABLE 4: Select Laboratory Abnormalities (>20%) Worsening from Baseline in Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma Who Received MONJUVI in L-MIND

Laboratory Abnormality	MONJUVI[1]	
	All Grades (%)	Grade 3 or 4 (%)
Chemistry		
Glucose increased	49	5
Calcium decreased	47	1.4
Gamma glutamyl transferase increased	34	5
Albumin decreased	26	0
Magnesium decreased	22	0
Urate increased	20	7
Phosphate decreased	20	5
Creatinine increased	20	1.4
Aspartate aminotransferase increased	20	0
Coagulation		
Activated partial thromboplastin time increased	46	4.1

[1]The denominator used to calculate the rate was 74 based on the number of patients with a baseline value and at least one post-treatment value.

6.2 Immunogenicity

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

Overall, no treatment-emergent or treatment-boosted anti-tafasitamab antibodies were observed. No clinically meaningful differences in the pharmacokinetics, efficacy, or safety profile of tafasitamab-cxix were observed in 2.5% of 81 patients with relapsed or refractory DLBCL with pre-existing anti-tafasitamab antibodies in L-MIND.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action, MONJUVI may cause fetal B-cell depletion when administered to a pregnant woman *[see Clinical Pharmacology (12.1)]*. There are no available data on MONJUVI use in pregnant women to evaluate for a drug-associated risk. Animal reproductive toxicity studies have not been conducted with tafasitamab-cxix.

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

MONJUVI is administered in combination with lenalidomide for up to 12 cycles. Lenalidomide can cause embryo-fetal harm and is contraindicated for use in pregnancy. Refer to the lenalidomide prescribing information for additional information. Lenalidomide is only available through a REMS program.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Immunoglobulin G (IgG) monoclonal antibodies are transferred across the placenta. Based on its mechanism of action, MONJUVI may cause depletion of fetal CD19 positive immune cells. Defer administering live vaccines to neonates and infants exposed to tafasitamab-cxix in utero until a hematology evaluation is completed.

Data

Animal Data

Animal reproductive studies have not been conducted with tafasitamab-cxix. Tafasitamab-cxix is an IgG antibody and thus has the potential to cross the placental barrier permitting direct fetal exposure and depleting fetal B lymphocytes.

8.2 Lactation

Risk Summary

There are no data on the presence of tafasitamab-cxix in human milk or the effects on the breastfed child or milk production. Maternal immunoglobulin G is known to be present in human milk. The effects of local gastrointestinal exposure and limited systemic exposure in the breastfed infant to MONJUVI are unknown. Because of the potential for serious adverse reactions in the breastfed child, advise women not to breastfeed during treatment with MONJUVI and for at least 3 months after the last dose. Refer to lenalidomide prescribing information for additional information.

8.3 Females and Males of Reproductive Potential

MONJUVI can cause fetal B-cell depletion when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*.

Pregnancy Testing

Refer to the prescribing information for lenalidomide for pregnancy testing requirements prior to initiating the combination of MONJUVI with lenalidomide.

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment with MONJUVI and for at least 3 months after the last dose. Additionally, refer to the lenalidomide prescribing information for additional recommendations for contraception.

Males

Refer to the lenalidomide prescribing information for recommendations.

8.4 Pediatric Use

The safety and effectiveness of MONJUVI in pediatric patients have not been established.

8.5 Geriatric Use

Among 81 patients who received MONJUVI and lenalidomide in L-MIND, 72% were 65 years and older, while 38% were 75 years and older. Clinical studies of MONJUVI did not include sufficient numbers of patients aged 65 and older to determine whether effectiveness differs compared to that of younger subjects. Patients 65 years and older had more serious adverse reactions (57%) than younger patients (39%).

11 DESCRIPTION

Tafasitamab-cxix is a humanized CD19-directed cytolytic monoclonal antibody that contains an IgG1/2 hybrid Fc-domain with 2 amino acid substitutions to modify the Fc-mediated functions of the antibody. It is produced by recombinant DNA technology in mammalian cells (Chinese hamster ovary). Tafasitamab-cxix has a molecular weight of approximately 150 kDa.

MONJUVI (tafasitamab-cxix) for injection is supplied as a sterile, preservative-free, white to slightly yellowish lyophilized powder in a single-dose vial for intravenous use after reconstitution and further dilution. After reconstitution with 5 mL of Sterile Water for Injection, USP, the resulting concentration is 40 mg/mL with a pH of 6.0. Each single-dose vial contains 200 mg tafasitamab-cxix, citric acid monohydrate (3.7 mg), polysorbate 20 (1 mg), sodium citrate dihydrate (31.6 mg) and trehalose dihydrate (378.3 mg).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Tafasitamab-cxix is an Fc-modified monoclonal antibody that binds to CD19 antigen expressed on the surface of pre-B and mature B lymphocytes and on several B-cell malignancies, including diffuse large B-cell lymphoma (DLBCL).

Upon binding to CD19, tafasitamab-cxix mediates B-cell lysis through apoptosis and immune effector mechanisms, including antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP).

In studies conducted in vitro in DLBCL tumor cells, tafasitamab-cxix in combination with lenalidomide resulted in increased ADCC activity compared to tafasitamab-cxix or lenalidomide alone.

12.2 Pharmacodynamics

Tafasitamab-cxix reduced peripheral blood B cell counts by 97% after eight days of treatment in patients with relapsed or refractory DLBCL. Nadir, with a reduction of 100%, was reached within 16 weeks of treatment.

12.3 Pharmacokinetics

Mean trough concentrations (± standard deviation) were 179 (± 53) µg/mL following administration of MONJUVI at 12 mg/kg on Days 1, 8, 15, and 22 in Cycle 1-3 (plus an additional dose on Cycle 1 Day 4), and 153 (± 68) µg/mL following administration of MONJUVI at 12 mg/kg on Days 1 and 15 from Cycle 4 onwards. Overall maximum tafasitamab-cxix serum concentrations were 483 (±109) µg/mL.

Distribution

The total volume of distribution for tafasitamab-cxix was 9.3 L (95% CI: 8.6, 10 L).

Elimination

The clearance of tafasitamab-cxix was 0.41 L/day (CV: 32%) and terminal elimination half-life was 17 days (95% CI: 15, 18 days).

Specific Populations

Bodyweight (40 to 163 kg) has a significant effect on the pharmacokinetics of tafasitamab-cxix, with higher clearance and volume of distribution expected with higher body weight. No clinically meaningful differences in the pharmacokinetics of tafasitamab-cxix were observed based on age (16 to 90 years), sex, mild to moderate renal impairment (CLcr 30-89 mL/min estimated by the Cockcroft-Gault equation), and mild hepatic impairment (total bilirubin ≤ ULN and AST > ULN, or total bilirubin 1 to 1.5 times ULN and any AST). The effect of severe renal impairment to end-stage renal disease (CLcr < 30 mL/min), moderate to severe hepatic impairment (total bilirubin > 1.5 times ULN and any AST), and race/ethnicity on tafasitamab-cxix pharmacokinetics is unknown.

Drug Interaction Studies

No clinically meaningful differences in tafasitamab-cxix pharmacokinetics were observed when used concomitantly with lenalidomide.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity and genotoxicity studies have not been conducted with tafasitamab-cxix.

Fertility studies have not been conducted with tafasitamab-cxix.

In the 13-week repeat-dose general toxicity study in cynomolgus monkeys, no adverse effects on male and female reproductive organs were observed up to the highest dose tested, 100 mg/kg/week (approximately 9 times the human exposure based on AUC at the clinical dose of 12 mg/kg/week).

14 CLINICAL STUDIES

The efficacy of MONJUVI in combination with lenalidomide followed by MONJUVI as monotherapy was evaluated in L-MIND, an open-label, multicenter, single arm trial (NCT02399085). Eligible patients had relapsed or refractory DLBCL after 1 to 3 prior systemic therapies, including a CD20-directed cytolytic antibody, and were not candidates for high dose chemotherapy (HDC) followed by autologous stem cell transplantation (ASCT). Patients received MONJUVI 12 mg/kg intravenously in combination with lenalidomide (25 mg orally on Days 1 to 21 of each 28-day cycle) for a maximum of 12 cycles, followed by MONJUVI as monotherapy until disease progression or unacceptable toxicity as follows:

- Cycle 1: Days 1, 4, 8, 15 and 22 of the 28-day cycle;
- Cycles 2 and 3: Days 1, 8, 15 and 22 of each 28-day cycle;
- Cycles 4 and beyond: Days 1 and 15 of each 28-day cycle.

Of the 71 patients with DLBCL confirmed by central laboratory who received the combination therapy, the median age was 71 years (range: 41 to 86 years); 55% were males, and 100% had received a prior CD20-containing therapy. Race was collected in 92% of patients; of these, 95% were White, and 3% were Asian. The median number of prior therapies was two; 49% had one prior line of treatment, and 51% had 2 to 4 prior lines. Thirty-two patients (45%) were refractory to their last prior therapy and 30 (42%) were refractory to rituximab. Nine patients (13%) had received prior ASCT. The primary reasons patients were not candidates for ASCT included age (47%), refractoriness to salvage chemotherapy (27%), comorbidities (13%) and refusal of high dose chemotherapy/ASCT (13%).

Efficacy was established based on best overall response rate, defined as the proportion of complete and partial responders, and duration of response, as assessed by an Independent Review Committee using the International Working Group Response Criteria (Cheson, 2007). Results are summarized in **Table 5**.

TABLE 5: Efficacy Results in L-MIND

	N = 71
Best overall response rate, n (%)	39 (55%)
(95% CI)	(43%, 67%)
Complete response rate	37%
Partial response rate	18%
Duration of Response	
Median (range) in months[a]	21.7 (0, 24)

[a]Kaplan Meier estimates

16 HOW SUPPLIED/STORAGE AND HANDLING

MONJUVI (tafasitamab-cxix) for injection is a sterile, preservative-free, white to slightly yellowish lyophilized powder for reconstitution supplied as a 200 mg single-dose vial.

Each 200 mg vial is individually packaged in a carton (NDC 73535–208–01).

Store refrigerated at 36°F to 46°F (2°C to 8°C) in the original carton to protect from light. Do not shake. Do not freeze.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Infusion-Related Reactions

Advise patients to contact their healthcare provider if they experience signs and symptoms of infusion-related reactions *[see Warnings and Precautions (5.1)]*.

Myelosuppression

Inform patients about the risk of myelosuppression. Advise patients to immediately contact their healthcare provider for a fever of 100.4°F (38°C) or greater or signs or symptoms of bruising or bleeding. Advise patients of the need for periodic monitoring of blood counts *[see Warnings and Precautions (5.2)]*.

Infections

Inform patients about the risk of infections. Advise patients to immediately contact their healthcare provider for a fever of 100.4°F (38°C) or greater or signs or symptoms of infection *[see Warnings and Precautions (5.3)]*.

Embryo-Fetal Toxicity

- Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.4), Use in Specific Population (8.1)]*.
- Advise females of reproductive potential to use effective contraception during treatment with MONJUVI and for at least 3 months after the last dose *[see Use in Specific Populations (8.3)]*.
- Advise patients that lenalidomide has the potential to cause fetal harm and has specific requirements regarding contraception, pregnancy testing, blood and sperm donation, and transmission in sperm. Lenalidomide is only available through a REMS program *[see Use in Specific Populations (8.1,8.3)]*.

Lactation

Advise women not to breastfeed during treatment with MONJUVI and for at least 3 months after the last dose *[see Use in Specific Populations (8.2)]*.

Manufactured by:
MORPHOSYS US INC.
Boston, MA 02210
U.S. License No. 2152

Marketed by:
MORPHOSYS US INC. and INCYTE Corporation.
MONJUVI is a registered trademark of MorphoSys AG

Product of Germany

PATIENT INFORMATION

MONJUVI® (mon-JOO-vee)
(tafasitamab-cxix)
for injection

What is MONJUVI?

MONJUVI is a prescription medicine given with lenalidomide to treat adults with certain types of diffuse large B-cell lymphoma (DLBCL) that has come back (relapsed) or that did not respond to previous treatment (refractory) and who cannot receive a stem cell transplant.

It is not known if MONJUVI is safe and effective in children.

Before you receive MONJUVI, tell your healthcare provider about all of your medical conditions, including if you:

- have an active infection or have had one recently.
- are pregnant or plan to become pregnant. MONJUVI may harm your unborn baby. You should not become pregnant during treatment with MONJUVI. Do not receive treatment with MONJUVI in combination with lenalidomide if you are pregnant because lenalidomide can cause birth defects and death of your unborn baby.
  - You should use an effective method of birth control (contraception) during treatment and for at least 3 months after your last dose of MONJUVI.
  - Tell your healthcare provider right away if you become pregnant or think you may be pregnant during treatment with MONJUVI.
- are breastfeeding or plan to breastfeed. It is not known if MONJUVI passes into your breastmilk. Do not breastfeed during treatment and for at least 3 months after your last dose of MONJUVI.

You should also read the lenalidomide Medication Guide for important information about pregnancy, contraception, and blood and sperm donation.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How will I receive MONJUVI?

- MONJUVI will be given to you by your healthcare provider as an intravenous (IV) infusion into one of your veins.
- Your healthcare provider will give you medicines before each infusion to decrease your chance of infusion reactions. If you do not have any reactions, your health care provider may decide that you do not need these medicines with later infusions.
- Each treatment cycle of MONJUVI lasts for 28 days.
- Your healthcare provider may need to delay or completely stop treatment with MONJUVI if you have severe side effects.
- Your healthcare provider will decide how many treatments you need.
- If you miss any appointments, call your healthcare provider as soon as possible to reschedule your appointment.

What are the possible side effects of MONJUVI?

MONJUVI may cause serious side effects, including:

- **Infusion reactions.** Your healthcare provider will monitor you for infusion reactions during your infusion of MONJUVI. Tell your healthcare provider right away if you get fever, chills, flushing, headache, or shortness of breath during an infusion of MONJUVI.
- **Low blood cell counts** (platelets, red blood cells, and white blood cells). Low blood cell counts are common with MONJUVI, but can also be serious or severe. Your healthcare provider will monitor your blood counts during treatment with MONJUVI. Tell your healthcare provider right away if you get a fever of 100.4°F (38°C) or above, or any bruising or bleeding.
- **Infections.** Serious infections, including infections that can cause death, have happened in people during treatment with MONJUVI and after the last dose. Tell your healthcare provider right away if you get a fever of 100.4°F (38°C) or above, or develop any signs or symptoms of an infection.

The most common side effects of MONJUVI include:

- feeling tired or weak
- diarrhea
- cough
- fever
- swelling of lower legs or hands
- respiratory tract infection
- decreased appetite

These are not all the possible side effects of MONJUVI.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of MONJUVI.

Medicines are sometimes prescribed for purposes other than those listed in this Patient Information. If you would like more information about MONJUVI, talk with your healthcare provider. You can ask your healthcare provider for information about MONJUVI that is written for health professionals.

What are the ingredients in MONJUVI?

Active ingredient: tafasitamab-cxix.

Inactive ingredients: citric acid monohydrate, polysorbate 20, sodium citrate dihydrate, and trehalose dihydrate.

Manufactured by: MORPHOSYS US INC., Boston, MA 02210, U.S. License No. 2152,
Marketed by: MORPHOSYS US INC. and INCYTE Corporation.

For more information call MorphoSys US Inc., at 1-844-667-1992 or go to www.MONJUVI.com.

This Patient Information has been approved by the U.S. Food and Drug Administration. Issued: JUN 2021

NATERA
NATERA

Greetings!

Thank you for taking some time to learn about Signatera. We are excited to introduce this new technology to oncologists and patients in Idaho.

Signatera is a custom-built circulating tumor DNA (ctDNA)test for treatment monitoring and molecular residual disease (MRD) assessment in patients previously diagnosed with cancer. Medicare issued a positive coverage determination for stage II-III colorectal cancer and a draft positive coveragef or pan cancer immune checkpoint inhibitor treatment monitoring.

The Signatera test is personalized and tumor-informed, providing each individual with a customized blood test tailored to fit the unique signature of clonal mutations found in that individual's tumor. This maximizes accuracy for detecting the presence or absence of residual disease in a blood sample, even at levels down to a single tumor molecule in a tube of blood.

Unlike a standard liquid biopsy, Signatera is not intended to match patients with any particular therapy; rather it is intended to detect and quantify how much cancer is left in the body, to detect recurrence earlier and help optimize treatment decisions. Signatera test performance has been clinically validated in multiple cancer types including colorectal, non-small cell lung, breast, and bladder cancers.

Please let us know if you would like to set up a time to and discuss further.

Sincerely,

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Regional Director
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MEDICARE COVERAGE

AFTER DEFINITIVE THERAPY IN CRC

Signatera™ looks deeper

- Does my patient need adjuvant chemotherapy?
- Is the treatment working?
- Is the cancer recurring?

A personalized, tumor-informed approach for molecular residual disease (MRD) detection

natera™ | Signatera™ Residual disease test (MRD)

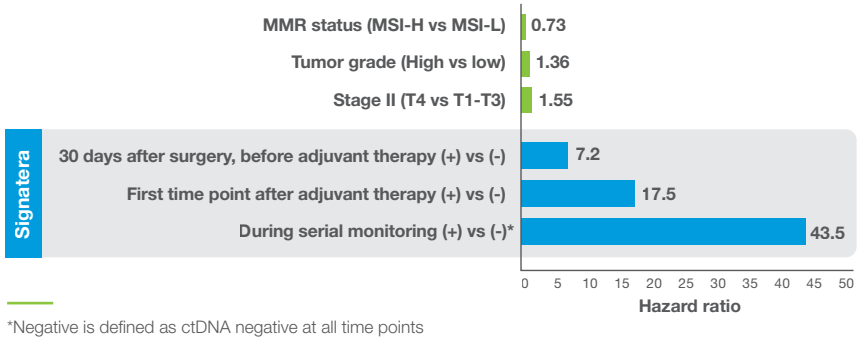
When to use Signatera

In the adjuvant setting

Use Signatera after surgery to evaluate the need for adjuvant chemotherapy and potentially avoid unnecessary treatment

Signatera accurately identifies patients at high risk of recurrence

Signatera MRD status outperforms known clinicopathologic risk factors in predicting relapse[1-4]



*Negative is defined as ctDNA negative at all time points

- 97% of patients with a positive Signatera result will relapse without additional treatment[1]
- Serial testing with Signatera improves sensitivity and negative predictive value of test results

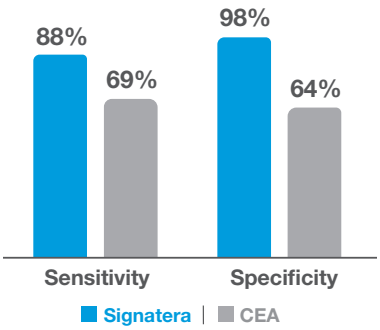
In the surveillance setting

Use Signatera along with CEA testing to detect recurrence earlier, while the tumor may still be resectable

Signatera detects relapse more accurately than CEA with clinically meaningful lead times over CT scans[1]

- Get clarity when evaluating patients with indeterminate CEA levels or CT scans
- Signatera facilitates shared decision-making and confident treatment planning

Accuracy in detecting relapse



Average lead time of ctDNA detection before CT scan

8.7

MONTHS

Maximum lead of 16.5 months

CEA = carcinoembryonic antigen; **CT** = computed tomography; **ctDNA** = circulating-tumor DNA

Decisions informed by the tumor for reliable MRD detection

Clinical utility of a Signatera ctDNA result

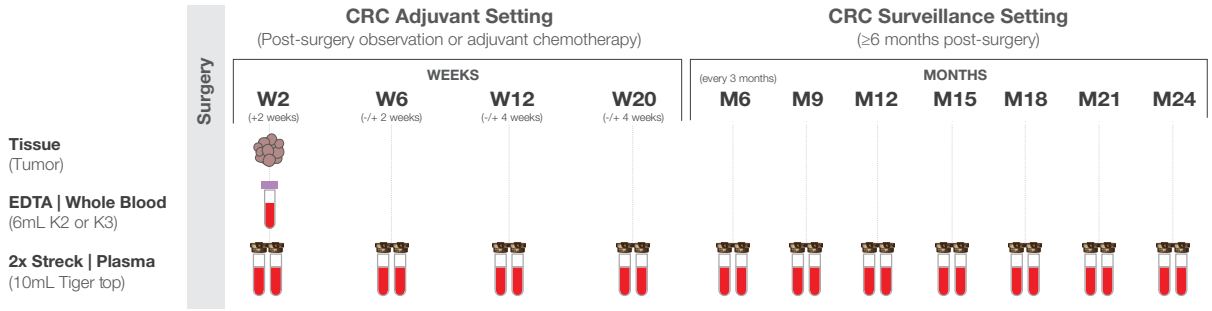
Adjuvant setting

	ctDNA high risk (+)	ctDNA low risk (−)
Stage II colon Stage IIA rectal	Manage as high risk	Risk similar to stage I, consider repeat testing and observation
Stage III colon	Manage as high risk	Consider repeat testing and de-escalation

Surveillance setting

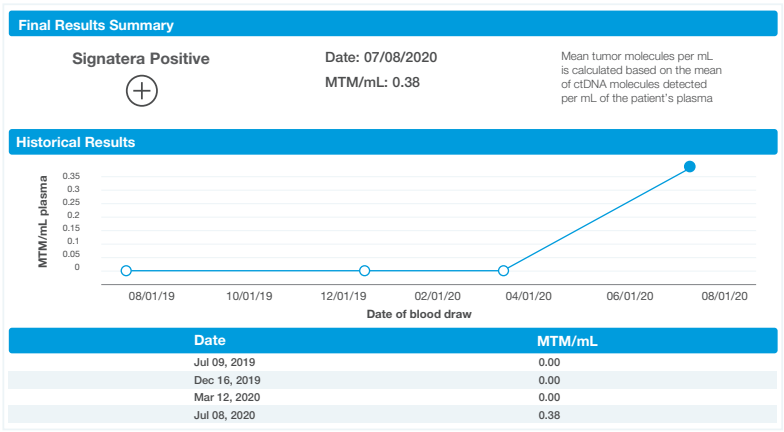
	ctDNA high risk (+)	ctDNA low risk (−)
Stage II and III colorectal	Consider more frequent CT scans or escalating to PET or MRI to locate disease while potentially resectable	Consider monitoring with reassurance

Recommended post-surgical draw schedules



- Medicare patients with stage II/III CRC are fully covered, for both serial and single time point use
- Turnaround times: Initial test design = 2-3 weeks; subsequent blood draws = 1 week

Quantitative ctDNA results enable longitudinal monitoring



- Signatera reports presence/absence of ctDNA and ctDNA quantity in terms of MTM/mL for longitudinal assessment
- Unlike other ctDNA assays, Signatera is designed to accurately detect MRD (i.e., not designed for early cancer screening nor for identifying actionable mutations for therapy selection)

MTM = mean tumor molecules

Just like no two tumors are alike—Signatera is personalized for each patient

Tumor-informed MRD assay for individualized care

- Customized for each patient's unique tumor signature by targeting the top clonal mutations

Optimized sensitivity and specificity for accurate MRD assessment

- By only tracking tumor-specific variants, sensitivity is maximized with a LOD down to 0.01% VAF[5]
- Filters out germline and CHIP mutations to reduce background noise and to minimize false positives

Reliable longitudinal monitoring for confident decision-making

- By following clonal mutations that persist as the tumor evolves, full disease burden is reflected
- Quantification of MRD by MTM/mL enables longitudinal monitoring with a simple blood draw

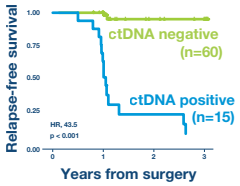
LOD = limit of detection; **CHIP** = clonal hematopoiesis of indeterminate potential; **VAF** = Varient allele frequency

Look deeper—so you can know sooner

Signatera is validated across multiple tumor types[1,5-7]

Colon[1]

JAMA Oncology

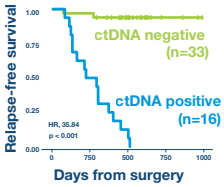


88%
sensitivity to relapse

Average lead time 8.7 mos

Breast[5]

Clinical Cancer Research

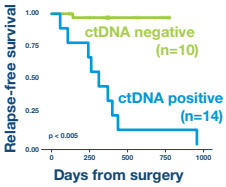


89%
sensitivity to relapse

Average lead time 9.5 mos

Lung[6]

NATURE

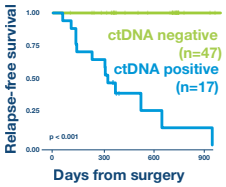


92%
sensitivity to relapse

Average lead time 4.0 mos

Bladder[7]

Journal of Clinical Oncology



100%
sensitivity to relapse

Average lead time 2.8 mos

References

1. Reinert T, Henriksen TV, Christensen E, et al. Analysis of Plasma Cell-Free DNA by Ultradeep Sequencing in Patients With Stages I to III Colorectal Cancer. *JAMA Oncol*. 2019. 2. Sinicrope FA, Foster NR, Thibodeau SN, et al. DNA Mismatch Repair Status and Colon Cancer Recurrence and Survival in Clinical Trials of 5-Fluorouracil-Based Adjuvant Therapy. *J Natl Cancer Inst.* 2011;103(11):863–875. 3. Aoyama, Oba K, Honda M, et al. Impact of postoperative complications on the colorectal cancer survival and recurrence: analyses of pooled individual patients' data from three large phase III randomized trials. *Cancer Med.* 2017;6(7):1573–1580. 4. Yothers G, O'Connell MJ, Lopatin M, et al. Validation of the 12-gene colon cancer recurrence score in NSABP C-07 as a predictor of recurrence in patients with stage II and III colon cancer treated with fluorouracil and leucovorin (FU/LV) and FU/LV plus oxaliplatin. *J Clin Oncol.* 2013;31(36):4512-4519. 5. Coombes RC, Page K, Salari R, et al. Personalized Detection of Circulating Tumor DNA Antedates Breast Cancer Metastatic Recurrence. *Clin Cancer Res.* 2019;25(14):4255-4263. 6. Abbosh C, Birkbak NJ, Wilson GA, et al. Phylogenetic ctDNA analysis depicts early-stage lung cancer evolution. *Nature.* 2017;545(7655):446-451. 7. Christensen E, Birkenkamp-Demtroder K, Sethi H, et al. Early Detection of Metastatic Relapse and Monitoring of Therapeutic Efficacy by Ultra-Deep Sequencing of Plasma Cell-Free DNA in Patients With Urothelial Bladder Carcinoma. *J Clin Oncol.* 2019;37(18):1547-1557.

Learn more about Signatera:

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13011 McCallen Pass, Building A Suite 100 | Austin, TX 78753 | www.natera.com | 1.650.489.9050 | Fax 1.650.412.1962

natera™

DURING TREATMENT WITH IMMUNE CHECKPOINT INHIBITORS

Signatera looks deeper

Is the treatment working?

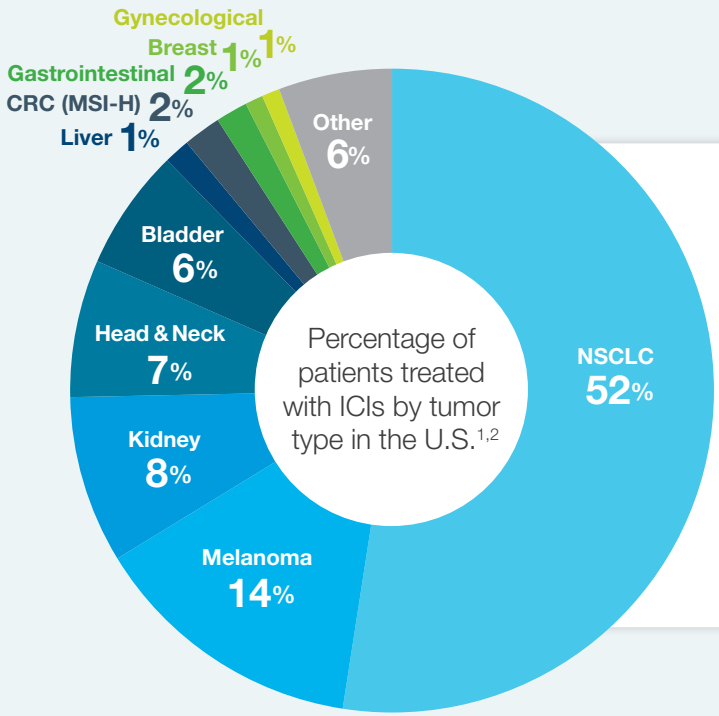
Is the tumor truly progressing?

Is there a need to change or reinitiate treatment?

Signatera™ is a personalized, tumor-informed assay for ultrasensitive detection of molecular residual disease (MRD)

natera™ | Signatera™
Residual disease test (MRD)

Early intelligence on therapy response can make a world of difference



<20%

of patients who receive immune checkpoint inhibitors will derive sustained response or clinical benefit[3]

Despite dramatic improvements in cancer care using immune checkpoint inhibitors (ICIs), only a minority of patients will benefit from ICI treatment.[3]

Better predictive tools for immunotherapy treatment response are needed

- Standard imaging tools lack the sensitivity to accurately assess pseudoprogression, which occurs in up to 10% of patients treated with immune checkpoint inhibitors[4]
- Tissue-based biomarkers, such as PD-L1 expression, TMB, and MSI-H/dMMR, have variable predictive value to ICI treatment[5-9]

Early biomarkers of treatment response could identify patients who are responding to immunotherapy.

dMMR=deficient mismatch repair; **MSI-H**=microsatellite instability high; **PD-L1**=programmed death-ligand 1; **TMB**=tumor mutational burden

The power of tumor-informed ctDNA detection

ctDNA is a real-time biomarker of tumor burden

- The effect of ICI treatment can be detected by measuring circulating tumor DNA (ctDNA) in the blood much earlier than it can be detected by CT scans or other serum protein biomarkers[10]
- A growing body of published studies across multiple solid tumor types supports using the dynamics of ctDNA during ICI treatment to monitor treatment response and to identify exceptional responders[11-17]

Signatera at a glance

Discover the personalized, tumor-informed approach behind Signatera

In patients with solid tumors receiving immune checkpoint inhibitors, use Signatera ctDNA trends to evaluate response and to optimize treatment duration in exceptional responders.

Tumor-informed approach is key for highly sensitive ctDNA monitoring

0.01% VAF is critical for achieving

baseline ctDNA detection

in patients with metastatic disease across 25 tumor types.[18]

Personalized, tumor informed assay

Tumor-specific, clonal mutations identified by whole-exome sequencing of the patient's tumor tissue to eliminate germline and CHIP mutations

Ultrasensitive ctDNA detection with multiplex PCR technology

Highly sensitive and specific, with a low limit of detection

Optimized for longitudinal monitoring

Only measures clonal mutations, which correlate with tumor burden

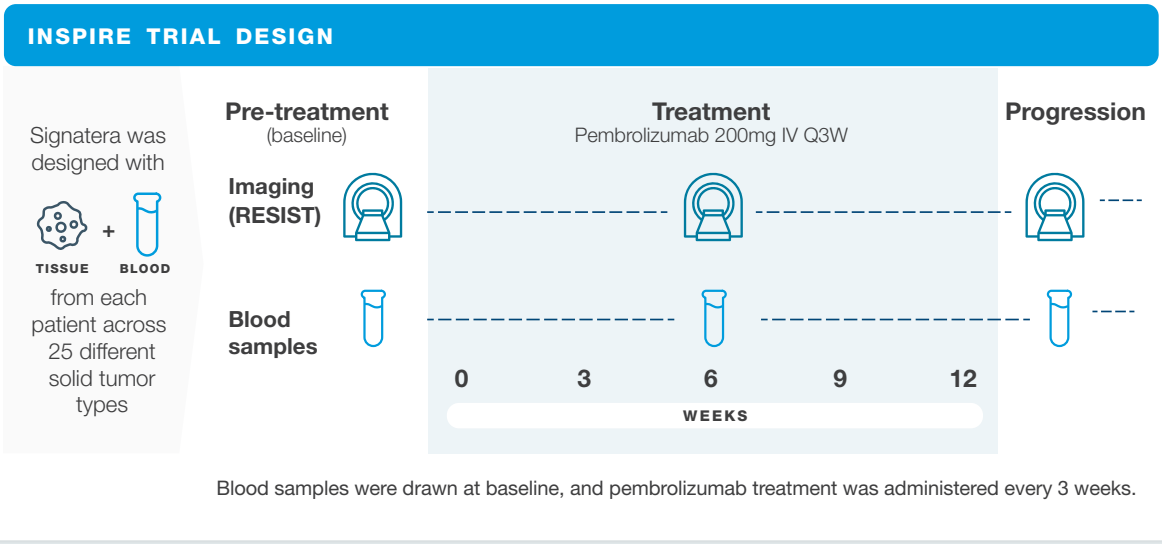
CHIP=clonal hematopoiesis of indeterminate potential; **CT**=computed tomography; **ctDNA**=circulating tumor DNA; **ICI**=immune checkpoint inhibitor; **VAF**=variant allele frequency

Real-time assessment of immunotherapy response

The Signatera assay was studied in a pan-cancer tumor cohort of patients receiving pembrolizumab treatment

The INSPIRE trial

The prospective phase II INSPIRE trial addressed clinically relevant issues related to the monitoring response to ICIs by assessing baseline ctDNA and ctDNA kinetics[18]



Blood samples were drawn at baseline, and pembrolizumab treatment was administered every 3 weeks.

As early as week 6, an increase in ctDNA level predicted a lack of response to pembrolizumab

98%

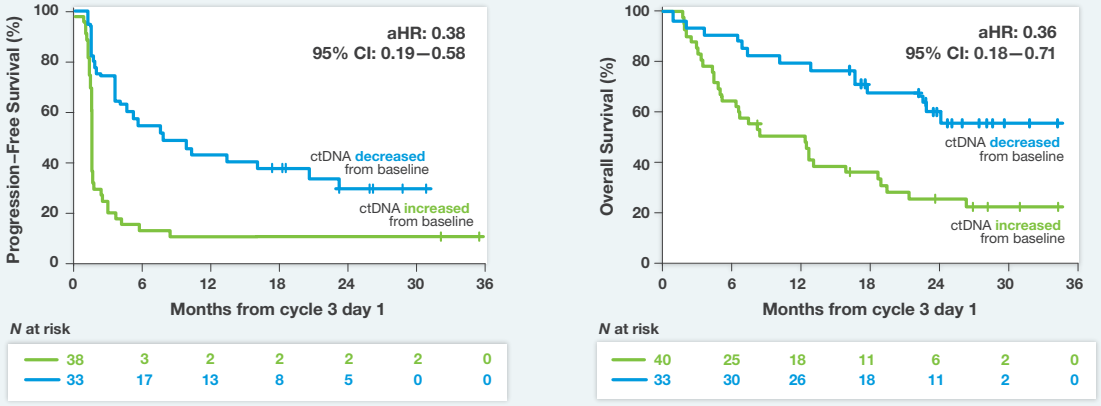
of patients (39/40) with an increase in ctDNA level at the beginning of cycle 3 did not have an objective response.[18]

None of the patients with an increase in both ctDNA and tumor size (n=30) achieved objective response at any time during the study.[18]

Decrease in ctDNA level at week 6 correlates with tumor response and favorable outcomes

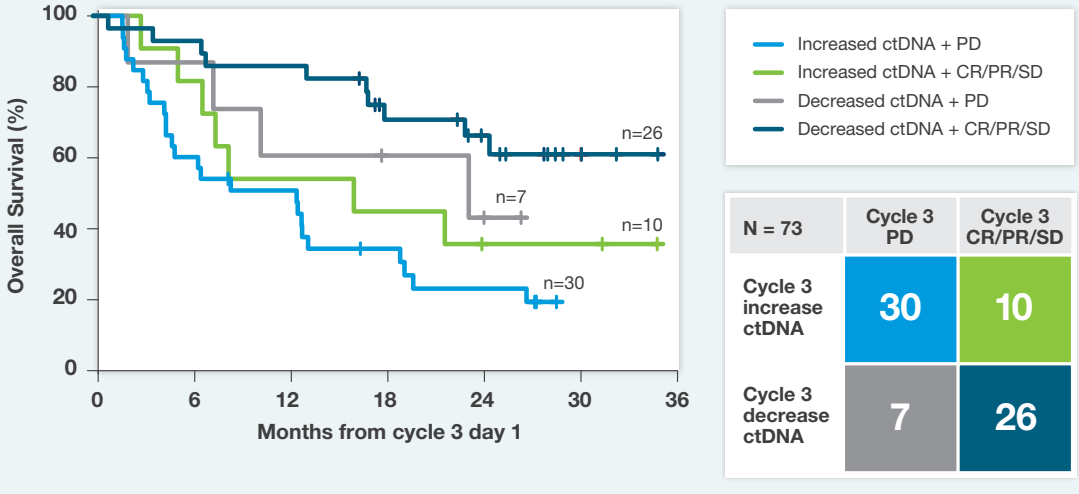
A decrease in ctDNA relative to baseline at the beginning of cycle 3 is a strong predictor of PFS and OS[18]

PFS and OS among patients with both baseline and cycle 3 ctDNA values, stratified according to increase or decrease of ctDNA



The addition of ctDNA monitoring to ICI response assessments can help improve OS predictions made by evaluation of tumor response by CT alone[18]

Risk groupings of patients identified by tumor response assessed on CT scans in conjunction with serial ctDNA values



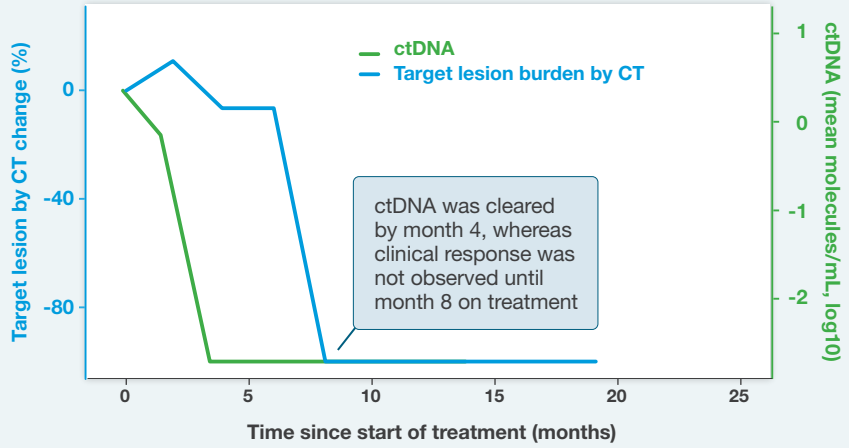
N = 73	Cycle 3 PD	Cycle 3 CR/PR/SD
Cycle 3 increase ctDNA	30	10
Cycle 3 decrease ctDNA	7	26

CR=complete response; **OS**=overall survival; **PD**=progressive disease; **PFS**=progression-free survival; **PR**=partial response; **SD**=stable disease

ctDNA is a sensitive and reliable molecular indicator of true progression

ctDNA dynamics precedes clinical response assessed by CT scans[18]

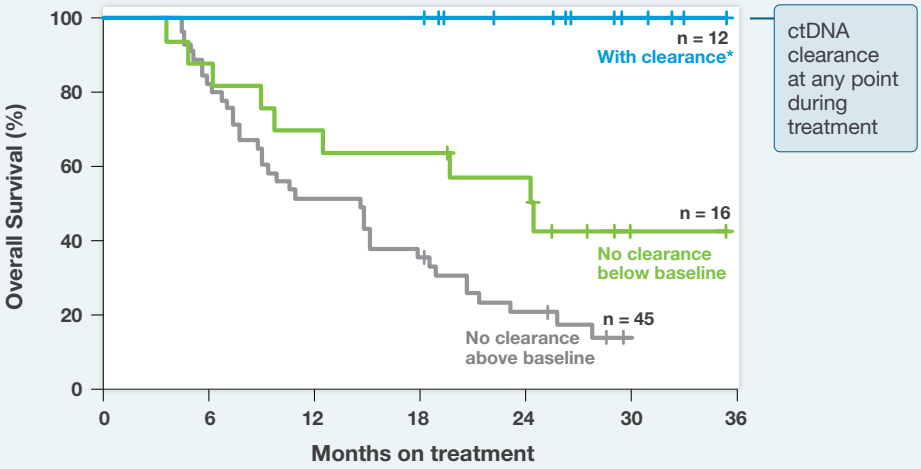
Patient with squamous cell carcinoma of the head and neck who experienced ctDNA clearance followed by durable clinical response



Achieving ctDNA clearance at any time during treatment correlates with durable OS

OS was 100% in patients who experienced ctDNA clearance for at least one on-treatment time point[18]

OS among patients with at least two ctDNA time points stratified by clearance of ctDNA



*Median follow-up beyond first clearance of 25.4 months (range 10.8-29.5)

Easy-to-interpret longitudinal report

Test report indicates the presence or absence of detectable ctDNA

FINAL RESULTS SUMMARY

Signatera Negative

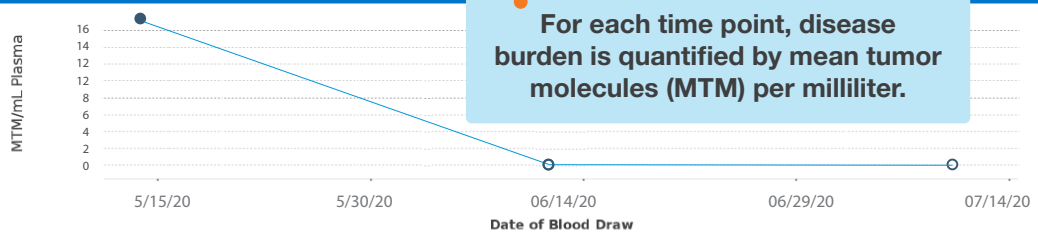
⊖

MTM/mL:
Not Detected

Mean tumor molecules per mL is calculated based on the mean of ctDNA molecules detected per mL of the patient's plasma.

Test Clinical Notes

Historical Results



For each time point, disease burden is quantified by mean tumor molecules (MTM) per milliliter.

Date	MTM/mL
Jul 09, 2020	0.00
Jun 12, 2020	0.00
May 14, 2020	16.96

Meet Natera's team of clinical experts who will support you and your patients

CLINICAL ONCOLOGY SPECIALISTS

- Main point of contact for requisition forms and kits
- Answer provider portal inquiries

CUSTOMER EXPERIENCE

- Acquires tumor tissue from pathology for whole-exome sequencing
- Answers test status inquiries from providers

ONCOLOGY CLINICAL INFORMATION

- Sets blood draw schedule for recurring orders
- Discusses test results with providers and availability of testing programs with providers and patients

PATIENT COORDINATORS

- Place welcome calls to patients
- Schedule mobile phlebotomy for Natera-managed blood draws
- Answer general billing inquiries and questions about compassionate care qualification
- Answer testing-related inquiries from patients

Look deeper – so you can know sooner

Evaluating response at key intervals during immunotherapy treatment is critical in informing decision-making and paving the way for stronger outcomes

- **98% of patients with metastatic disease across 25 tumor types had detectable ctDNA at baseline[18]**
- **Signatera ctDNA dynamics predicted tumor progression and correlated closely with treatment response to immune checkpoint inhibition[18]**
- **Clearance of ctDNA at any time is associated with 100% OS at up to 29.5 months of follow-up beyond first clearance[18]**

Use Signatera ctDNA monitoring for tumor-informed, response monitoring

- **Evaluate non-response at any point during treatment and plan for alternate options**
- **Help clarify indeterminate radiologic findings, including pseudoprogression**
- **Identify exceptional responders with ctDNA clearance**

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1. Haslam A, Gill J, Prasad V. Estimation of the Percentage of US Patients With Cancer Who Are Eligible for Immune Checkpoint Inhibitor Drugs. *JAMA Network Open*. 2020;3(3):e200423. doi:10.1001/jamanetworkopen.2020.0423. 2. *Global Oncology Trends* 2018. *IQVIA Institute for Human Data Science*. May 24, 2018. https://www.iqvia.com/insights/the-iqvia-institute/reports/global-oncology-trends-2018. Accessed on January 13, 2021. 3. Haslam A, Prasad V. Estimation of the Percentage of US Patients With Cancer Who Are Eligible for and Respond to Checkpoint Inhibitor Immunotherapy Drugs. *JAMA Network Open*. 2019;2(5):e192535-e192535. 4. Borcoman E, Nandikolla A, Long G, Goel S, Tourneau CL. Patterns of Response and Progression to Immunotherapy. *American Society of Clinical Oncology* Educational Book. 2018(38):169-178. 5. Melendez B, et al. Methods of measurement for tumor mutational burden in tumor tissue. *Transl Lung Cancer Res*. 2018;7(6):661-667. 6. Li L, et al. Promising clinical application of ctDNA in evaluating immunotherapy efficacy. *Am J Cancer Res.* 2018;8(10):1947-1956. 7. Kaderbhai C, et al. The role of molecular profiling to predict the response to immune checkpoint inhibitors in lung cancer. *Cancer.* 2019;11(2):201. 8. Berland L, Heeke S, Humber O, et al. Current views on tumor mutational burden in patients with non small cell lung cancer treated with immune checkpoint inhibitors. *J Thorac Dis*. 2019;11(Suppl 1): S71-S80. 9. Georgiadis A, et al. Noninvasive Detection of Microsatellite Instability and High Tumor Mutation Burden in Cancer Patients Treated with PD-1 Blockade. *Clin Cancer Res*. 2019;25(23):7024-7034. doi: 10.1158/1078-0432.CCR-19-1372. 10.Corcoran RB, Chabner BA. *N Engl J Med*. 2018;379(18):1754-1765. doi: 10.1056/NEJMra1706174. 11. Cabel L, Proudhon C, Romano E, et al. Clinical potential of circulating tumour DNA in patients receiving anticancer immunotherapy. *Nat Rev Clin Oncol*. 2018;15(10):639-650. 12. Goldberg SB, Narayan A, Kole AJ, et al. Early Assessment of Lung Cancer Immunotherapy Response via Circulating Tumor DNA. *Clin Cancer Res*. 2018;24(8):1872-1880. 13. Lee JH, Long GV, Menzies AM, et al. Association Between Circulating Tumor DNA and Pseudoprogression in Patients With Metastatic Melanoma Treated With Anti-Programmed Cell Death 1 Antibodies. *JAMA Oncol.* 2018;4(5):717-721. 14. Lee JH, Long GV, Boyd S, et al. Circulating tumour DNA predicts response to anti-PD1 antibodies in metastatic melanoma. *Ann Oncol.* 2017;28(5):1130-1136. 15. Raja R, Kuziora M, Brohawn PZ, et al. Early Reduction in ctDNA Predicts Survival in Patients with Lung and Bladder Cancer Treated with Durvalumab. *Clin Cancer Res*.2018;24(24):6212-6222. 16. Hellmann MD, Nabet BY, Rizvi H, et al. Circulating Tumor DNA Analysis to Assess Risk of Progression after Long-term Response to PD-(L)1 Blockade in NSCLC. *Clin Cancer Res.* 2020;26(12):2849-2858. 17. Zhang Q, Luo J, Wu S, et al. Prognostic and predictive impact of circulating tumor DNA in patients with advanced cancers treated with immune checkpoint blockade. *Cancer Discov.* 2020. DOI: 10.1158/2159-8290.CD-20-0047. 18. Bratman SV, Yang SYC, Iafolla MAJ, et al. Personalized circulating tumor DNA analysis as a predictive biomarker in solid tumor patients treated with pembrolizumab. *Nat Cancer.* 2020;1:873–881. https://doi.org/10.1038/s43018-020-0096-5

Learn more about Signatera:

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Waltham, MA 02541, USA

Pepaxto®

(melphalan flufenamide)

injection for intravenous use 20 mg/vial

Prescribing Information

FEBRUARY 2021

FULL PRESCRIBING INFORMATION: CONTENTS

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use PEPAXTO safely and effectively. See full prescribing information for PEPAXTO.

PEPAXTO® (melphalan flufenamide) for injection, for intravenous use
Initial U.S. Approval: 2021

----------INDICATIONS AND USAGE----------
PEPAXTO is an alkylating drug indicated in combination with dexamethasone, for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior lines of therapy and whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and one CD38-directed monoclonal antibody. (1)

This indication is approved under accelerated approval based on response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s). (1)

Limitations of Use: PEPAXTO is not indicated and is not recommended for use as a conditioning regimen for transplant outside of controlled clinical trials. (1, 5.5)

----------DOSAGE AND ADMINISTRATION----------
- Recommended dosage of PEPAXTO is 40 mg intravenously over 30 minutes on Day 1 of each 28-day treatment cycle, in combination with dexamethasone. (2.1)
- See Full Prescribing Information for instructions on preparation and administration. (2.4)

----------DOSAGE FORMS AND STRENGTHS----------
For injection: 20 mg melphalan flufenamide as a lyophilized powder in single-dose vial for reconstitution and dilution. (3)

----------CONTRAINDICATIONS----------
History of serious hypersensitivity reaction to melphalan flufenamide or melphalan. (4)

----------WARNINGS AND PRECAUTIONS----------
- Thrombocytopenia: Monitor platelet counts at baseline, during treatment, and as clinically indicated. Dose delay or dose reduction may be required to allow recovery of platelets. (2.3, 5.1)
- Neutropenia: Monitor neutrophil counts at baseline, during treatment and as clinically indicated. Monitor patients with neutropenia for signs of infection. Dose delay or dose reduction may be required to allow recovery of neutrophils. (2.3, 5.2)
- Anemia: Monitor red blood cell counts at baseline, during treatment, and as clinically indicated. (5.3)
- Infections: Monitor for signs/symptoms of infection and treat promptly. (5.4)
- Increased Risk of Mortality with PEPAXTO at Dosages Higher than the Recommended Dosage: Dosages exceeding the recommended dose for PEPAXTO may be associated with mortality. (1, 5.5, 13.2)
- Secondary Malignancies: Monitor patients long-term for the development of secondary malignancies. (5.6)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise patients of reproductive potential of the potential risk to a fetus and to use effective contraception. (5.7, 8.1, 8.3)

----------ADVERSE REACTIONS----------
Most common adverse reactions (> 20%) are fatigue, nausea, diarrhea, pyrexia and respiratory tract infection. (6.1)
Most common laboratory abnormalities (≥50%) are leukocytes decrease, platelets decrease, lymphocytes decrease, neutrophils decrease, hemoglobin decrease and creatinine increase. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Oncopeptides Inc at 1-866-522-8894 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------USE IN SPECIFIC POPULATIONS----------
Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 2/2021

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- 2.1 Recommended Dosage
- 2.2 Recommended Premedication and Concomitant Medication
- 2.3 Dosage Modification for Adverse Reactions
- 2.4 Preparation and Administration

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

PEPAXTO is indicated in combination with dexamethasone for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior lines of therapy and whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and one CD38-directed monoclonal antibody.

This indication is approved under accelerated approval based on response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s) *[see Clinical Studies (14)]*.

Limitations of Use

PEPAXTO is not indicated and is not recommended for use as a conditioning regimen for transplant outside of controlled clinical trials *[see Warnings and Precautions (5.5)].*

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dosage of PEPAXTO is 40 mg administered intravenously over 30 minutes on Day 1 of each 28-day cycle until disease progression or until unacceptable toxicity. Administer dexamethasone 40 mg orally or intravenously on Days 1, 8, 15 and 22 of each cycle. For patients 75 years of age or older, reduce the dose of dexamethasone to 20 mg. Refer to the prescribing information for dexamethasone for additional dosing information *[see Clinical Studies (14)]*.

2.2 Recommended Premedication and Concomitant Medications

Consider providing a serotonin-3 (5-HT3) receptor antagonist or other antiemetics prior to and during the treatment with PEPAXTO.

2.3 Dosage Modifications for Adverse Reactions

Withold PEPAXTO if the neutrophil count is less than 1 x 10^9/L or the platelet count is less than 50 x 10^9/L.

The recommended dose reductions and dosage modifications for adverse reactions for PEPAXTO are presented in Table 1 and Table 2, respectively.

Table 1: Recommended Dose Reductions for Adverse Reactions of PEPAXTO

Dose Reduction	Dosage*
First	30 mg
Second	20 mg
Subsequent	Permanently discontinue PEPAXTO in patients who are unable to tolerate 20 mg.

* Administered intravenously on Day 1 of each 28-day cycle. For dosage modifications, see Table 2.

Table 2: Recommended Dosage Modifications for Adverse Reactions of PEPAXTO

Adverse Reaction	Severity	Dosage Modification
Myelosuppression *[see Warnings and Precautions (5.1, 5.2)]*	Platelet count less than 50 x 10^9/L on an intended PEPAXTO dosing day	• Withhold PEPAXTO and monitor platelet count weekly until platelet count is 50 x 10^9/L or greater. • Resume PEPAXTO - at same dose if delay is 2 weeks or less. - at 1 dose level lower if delay is more than 2 weeks.
	Absolute neutrophil count less than 1 x 10^9/L on an intended PEPAXTO dosing day	• Withhold PEPAXTO and monitor neutrophil count weekly until neutrophil count is 1 x 10^9/L or greater. • Resume PEPAXTO - at same dose if delay is 2 weeks or less. - at 1 dose level lower if delay is more than 2 weeks.

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Adverse Reaction	Severity	Dosage Modification
	Grade 4 hematological adverse reaction on an intended PEPAXTO dosing day in 2 consecutive cycles	• Resume PEPAXTO at 1 dose level lower.
Non-Hematologic Adverse Reaction *[see Adverse Reactions (6.1)]*	Grade 2	• Consider withholding PEPAXTO until resolved to at least Grade 1 or baseline. • Consider resuming PEPAXTO at 1 dose level lower.
	Grade 3 or 4	• Withhold PEPAXTO until resolved to at least Grade 1 or baseline. • Resume PEPAXTO at 1 dose level lower as clinically appropriate.

2.4 Preparation and Administration

PEPAXTO is a hazardous drug. Follow applicable special handling and disposal procedures.[1]

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if visibly opaque particles, discoloration or foreign particles are observed.

Reconstitute and dilute PEPAXTO prior to infusion.

Additional agents required for preparation:

- 5% Dextrose Injection, USP (room temperature)
- 250 mL bag of **cold (2°C to 8°C / 36°F to 46°F)** 0.9% Sodium Chloride Injection, USP (refrigerate for at least 4 hours)

Preparation Steps:

Read the complete instructions prior to starting preparation.
Steps 3 to 5 must be completed within 30 minutes.

Reconstitution and dilution steps
Step 1 Determine the dose, the total volume of reconstituted PEPAXTO solution required, and the number of PEPAXTO vials needed. More than one vial may be needed for a full dose. Place PEPAXTO vial(s) at room temperature for at least 30 minutes.
Step 2 Shake the vial(s) vigorously or vortex to disintegrate the lyophilized PEPAXTO powder cake into a loose powder.
Step 3 to 5 must be completed within 30 minutes
Step 3 Aseptically reconstitute each vial with 40 mL of 5% Dextrose Injection, USP to obtain a final concentration of 0.5 mg/mL. Ensure the 5% Dextrose Injection, USP is room temperature (20°C to 25°C / 68°F to 77°F). Shake the vial(s) vigorously until solution is clear. Let the vial(s) stand to allow air bubbles to dissipate to confirm a clear solution.
Step 4 Withdraw 80 mL from a refrigerated (2°C to 8°C / 36°F to 46°F) 250 mL infusion bag of 0.9% Sodium Chloride Injection, USP. Discard the withdrawn 80 mL.
Step 5 Withdraw the required volume of reconstituted solution from the PEPAXTO vial(s) and transfer into an intravenous bag containing 0.9% Sodium Chloride Injection, USP to obtain a final concentration of 0.1 mg/mL to 0.16 mg/mL. Discard any unused portion left in the vial(s). Gently invert the bag to mix the solution. Do not shake. Check that the PEPAXTO solution is clear and colorless to pale yellow. Do not use if solution discoloration or particles are observed.

FULL PRESCRIBING INFORMATION: CONTENTS

Storage timelines:
PEPAXTO degrades in solution, especially at room temperature, and the storage timelines for diluted solution should not be exceeded:

For immediate administration:
Infusion of the diluted PEPAXTO solution must begin **within 60 minutes** of start of reconstitution (step 3).
For delayed administration:
If not used for immediate administration, the diluted PEPAXTO solution should be placed in a refrigerator (2°C to 8°C / 36°F to 46°F) within 30 minutes after initial reconstitution (step 3) and store for **up to 6 hours.**

Administration:
Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if visibly opaque particles, discoloration or foreign particles are observed.

Administration steps
Step 6 Administer PEPAXTO as a 30-minute intravenous infusion via a central venous access device, for example mediport, PICC or tunneled central venous catheter. If the infusion bag has been stored in a refrigerator, allow to reach to room temperature (20°C to 25°C / 68°F to 77°F). Start infusion within 30 minutes of removing the diluted PEPAXTO solution from the refrigerator.
Step 7 Administer PEPAXTO as an intravenous infusion via a central catheter over 30 minutes.
Step 8 Upon completion of PEPAXTO infusion, flush the central catheter per individual institutional guidelines.

3 DOSAGE FORMS AND STRENGTHS
For Injection: 20 mg melphalan flufenamide as a sterile lyophilized white to off-white powder in a single-dose vial for reconstitution and further dilution.

4 CONTRAINDICATIONS
PEPAXTO is contraindicated in patients with a history of serious hypersensitivity reaction to melphalan flufenamide or melphalan *[see Adverse Reactions (6.1)]*.

5 WARNINGS AND PRECAUTIONS
5.1 Thrombocytopenia
Thrombocytopenia was reported in 99% of 157 patients who received PEPAXTO with dexamethasone. Grade 3 thrombocytopenia was reported in 26% and Grade 4 thrombocytopenia was reported in 54% of patients *[see Adverse Reactions (6.1)].* Thrombocytopenia may lead to hemorrhage. Any Grade hemorrhage was reported in 28% of 157 patients. Grade 3 hemorrhage was reported in 3.2% and Grade 4 hemorrhage was reported in <1% of patients *[see Adverse Reactions (6.1)]*.

Grade 3 or 4 thrombocytopenia occurred in 43% of patients during the first cycle, with a median time to onset of 15 days from the first dose.

Monitor platelets at baseline, during treatment, and as clinically indicated. Monitor more frequently during the first two months of treatment with PEPAXTO. Do not administer PEPAXTO if the platelet count is less than 50 x 10^9/L. Withhold PEPAXTO until platelet count 50 x 10^9/L or greater and resume at same or reduced dose based on duration of interruption. Adjust dose and/or dose schedule based on signs and symptoms of bleeding *[see Dosage and Administration (2.3)].*

FULL PRESCRIBING INFORMATION: CONTENTS

5.2 Neutropenia

Neutropenia was reported in 95% of 157 patients who received PEPAXTO with dexamethasone. Grade 3 neutropenia was reported in 41% and Grade 4 neutropenia was reported in 40% of patients. Febrile neutropenia was reported in 6% of patients *[see Adverse Reactions (6.1)]*. Neutropenia may lead to infection.

Grade 3 or 4 neutropenia occurred in 50% during the first cycle, with a median time to onset of 15 days from the first dose.

Monitor neutrophil counts at baseline, during treatment, and as clinically indicated. Monitor more frequently during the first two months of treatment with PEPAXTO. Do not administer PEPAXTO if absolute neutrophil count less than 1 x 10^9/L. Withhold PEPAXTO until absolute neutrophil count is 1 x 10^9/L or greater and resume at same or reduced dose based on duration of interruption *[see Dosage and Administration (2.3)]*. Consider leukocyte growth factor as clinically appropriate.

5.3 Anemia

Anemia was reported in 84% of 157 patients who received PEPAXTO with dexamethasone. Grade 3 anemia was reported in 50% of 157 patients *[see Adverse Reactions (6.1)].*

Monitor red blood cell counts at baseline, during treatment, and as clinically indicated. Monitor more frequently during the first two months of treatment with PEPAXTO. Treat anemia as clinically indicated and as per standard guidelines. Dosage modification and dose delay of PEPAXTO may be required to allow for recovery of red blood cells.

5.4 Infections

Fatal infections were reported in <1% of 157 patients who received PEPAXTO with dexamethasone. Any Grade infection was reported in 58% of 157 patients who received PEPAXTO and dexamethasone. Grade 3 infections were reported in 20% and Grade 4 infection was reported in 1.9% of patients. Respiratory tract infection occurred in 24% (Grade ≥3 in 5%), pneumonia in 13% (Grade ≥3 in 11%), and sepsis in 3.8% (Grade ≥3 in 3.2%) of patients *[see Adverse Reactions (6.1)]*. Consider antimicrobials as clinically appropriate.

5.5 Increased Risk of Mortality with PEPAXTO at Dosages Higher than the Recommended Dosage

A nonclinical safety study in dogs with melphalan flufenamide at dosages exceeding the recommended dose for relapsed or refractory multiple myeloma was associated with mortality *[see Nonclinical Toxicology (13.2)]*. There is limited clinical experience of PEPAXTO at dosages higher than recommended. The safety and efficacy of PEPAXTO has not been established for use as a conditioning regimen in patients receiving transplant.

5.6 Secondary Malignancies

Secondary malignancies such as myelodysplastic syndromes or acute leukemia have occurred in patients with multiple myeloma who have received PEPAXTO. Monitor patients long-term for the development of secondary malignancies.

5.7 Embryo-Fetal Toxicity

Based on its mechanism of action, PEPAXTO can cause fetal harm when administered to a pregnant woman because it is genotoxic and targets actively dividing cells. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with PEPAXTO and for 6 months after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with PEPAXTO and for 3 months after the last dose *[see Use In Specific Populations (8.1, 8.3)]*.

6 ADVERSE REACTIONS

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

- Thrombocytopenia *[see Warnings and Precautions (5.1)].*
- Neutropenia *[see Warnings and Precautions (5.2)].*
- Anemia *[see Warnings and Precautions (5.3)].*
- Infections *[see Warnings and Precautions (5.4)]*.

FULL PRESCRIBING INFORMATION: CONTENTS

6.1 Clinical Trials Experience

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

Relapsed Refractory Multiple Myeloma (RRMM)

The safety of PEPAXTO was evaluated in HORIZON *[see Clinical Studies (14)]*. Patients received PEPAXTO 40 mg intravenously on Day 1 of each 28-day cycle, in combination with dexamethasone 40 mg orally (or 20 mg for patients 75 years and older) on Days 1, 8, 15 and 22 of each cycle (N=157). Patients were enrolled if they had absolute neutrophil count of 1 x 10^9/L or higher and platelet count of 75 x 10^9/L or greater. Among patients who received PEPAXTO, 29% were exposed for 6 months or longer and 6% were exposed for greater than one year.

Serious adverse reactions occurred in 49% of patients who received PEPAXTO. Serious adverse reactions in >3% of patients included pneumonia (10%), respiratory tract infection (6%), thrombocytopenia (5%), febrile neutropenia (5%) and sepsis (3.2%). Fatal adverse reactions occurred in 10 patients (6%) who received PEPAXTO, where general physical health deterioration (1.9%) and respiratory failure (1.3%) represented more than 1%.

Permanent discontinuation of PEPAXTO due to an adverse reaction occurred in 22% of patients. Adverse reactions which resulted in permanent discontinuation of PEPAXTO in >3% of patients included thrombocytopenia (11%).

Dosage interruptions of PEPAXTO due to an adverse reaction occurred in 62% of patients. The adverse reactions which resulted in dosage interruption of PEPAXTO in >3% of patients included thrombocytopenia (43%), neutropenia (29%), anemia (10%), respiratory tract infection (7%), leukopenia (6%) and pyrexia (4.5%).

Dose reductions of PEPAXTO due to an adverse reaction occurred in 27% of patients. Adverse reactions which resulted in dose reductions of PEPAXTO in >3% patients included thrombocytopenia (22%) and neutropenia (6%).

The most common adverse reactions (≥20%) were fatigue, nausea, diarrhea, pyrexia and respiratory tract infection. The most common laboratory abnormalities (≥50%) were leukocytes decreased, platelets decreased, lymphocytes decreased, neutrophils decreased, hemoglobin decreased and creatinine increased.

Table 3 summarizes the adverse reactions in HORIZON.

Table 3: Adverse reactions (≥10%) in Patients with RRMM Who Received PEPAXTO with Dexamethasone in HORIZON

Adverse Reaction	PEPAXTO with Dexamethasone (N=157)	
	All Grades (%)	Grade 3 or 4 (%)
General disorders and administration site disorders		
Fatigue[1]	55	6
Pyrexia[2]	24	1.9
Edema peripheral[2]	14	1.3
Gastrointestinal disorders		
Nausea[2]	32	0.6
Diarrhea	27	0
Constipation[2]	15	0.6
Vomiting	13	0
Infections		
Respiratory tract infection[2,3]	24	5
Pneumonia[4]	13	11

FULL PRESCRIBING INFORMATION: CONTENTS

Adverse Reaction	PEPAXTO with Dexamethasone (N=157)	
	All Grades (%)	**Grade 3 or 4 (%)**
Respiratory, thoracic and mediastinal disorders		
Cough[2]	17	0
Dyspnea[2]	11	1.3
Dyspnea exertional	10	0
Metabolism and nutrition disorders		
Decreased appetite[2]	14	0.6
Hypokalemia[2]	14	1.3
Hypocalcemia[2]	10	0.6
Nervous system disorders		
Headache	13	0
Dizziness	11	0
Musculoskeletal and connective tissue disorders		
Bone pain[2]	13	1.9
Pain in extremity[2]	13	1.9
Back pain[2]	12	0.6
Arthralgia	10	0
Psychiatric disorders		
Insomnia[2]	11	0.6

[1] Fatigue incudes fatigue and asthenia
[2] No Grade 4 adverse reactions occurred
[3] Respiratory tract infection includes upper respiratory tract infection, lower respiratory tract infection, respiratory tract infection and respiratory tract infection viral
[4] Pneumonia includes pneumonia, pneumocystis jirovecii pneumonia and pneumonia viral

Clinically relevant adverse reactions in <10% of patients who received PEPAXTO in combination with dexamethasone (N=157) included:

Allergic conditions: hypersensitivity reaction (7%)

Blood and lymphatic system disorders: febrile neutropenia (6%)

Infections: sepsis (3.8%)

Hemorrhages: Grade 3 or 4 hemorrhages (3.8%)

Table 4 summarizes the laboratory abnormalities in HORIZON.

Table 4: Laboratory Abnormalities (≥50%) That Worsened from Baseline in Patients in HORIZON

Laboratory Abnormality	PEPAXTO with Dexamethasone[1]	
	All Grades[2] (%)	**Grade 3-4[3] (%)**
Leukocytes decrease	99	88
Platelets decrease	99	80
Lymphocytes decrease	97	95
Neutrophils decrease	95	82
Hemoglobin decrease	84	50
Creatinine increase	68	1[4]

[1] Denominators for percentages are the number of patients with assessments at baseline and post-baseline (N=157 for all abnormalities)
[2] Patients with any worsening grade
[3] Patients with worsening to Grade 3 or 4, respectively
[4] No Grade 4 laboratory abnormality occurred

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8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action *[see Clinical Pharmacology (12.1)],* PEPAXTO can cause fetal harm when administered to a pregnant woman. There are no available data on PEPAXTO use in pregnant women to evaluate for a drug-associated risk. PEPAXTO is a genotoxic drug *[see Nonclinical Toxicology (13.1)]*. Advise pregnant women of the potential risk to a fetus.

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

Data

Animal Data

Animal reproductive or developmental toxicity studies were not conducted with PEPAXTO. Melphalan flufenamide is genotoxic and was toxic to actively dividing cells in animal studies and thus it has the potential to cause teratogenicity and embryo-fetal lethality.

8.2 Lactation

Risk Summary

There is no data on the presence of melphalan flufenamide or its metabolites in human breast milk, or the effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions in the breastfed child, advise women not to breastfeed during treatment with PEPAXTO and for 1 week after the last dose.

8.3 Females and Males of Reproductive Potential

PEPAXTO can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1*)].

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating PEPAXTO*.*

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment with PEPAXTO and for 6 months after the last dose.

Males

Based on genotoxicity findings, advise males with female partners of reproductive potential to use effective contraception during treatment with PEPAXTO and for 3 months after the last dose [*see Nonclinical Toxicology (13.1)*].

Infertility

Females

PEPAXTO can cause amenorrhea in premenopausal women and result in infertility.

Males

Based on findings of melphalan flufenamide in animals, PEPAXTO may impair male fertility [*see Nonclinical Toxicology (13.1)*]. Alkylating drugs, such as PEPAXTO, can also cause irreversible testicular suppression in patients.

8.4 Pediatric Use

The safety and effectiveness of PEPAXTO have not been established in pediatric patients.

8.5 Geriatric Use

Of the 157 patients with RRMM who received PEPAXTO, 50% were 65 years and older, while 16% were 75 years and older. No overall differences in safety were observed between these patients and younger patients. Clinical studies of PEPAXTO in patients with RRMM did not include sufficient numbers of patients 65 years of age and older to determine if they respond differently from younger adult patients.

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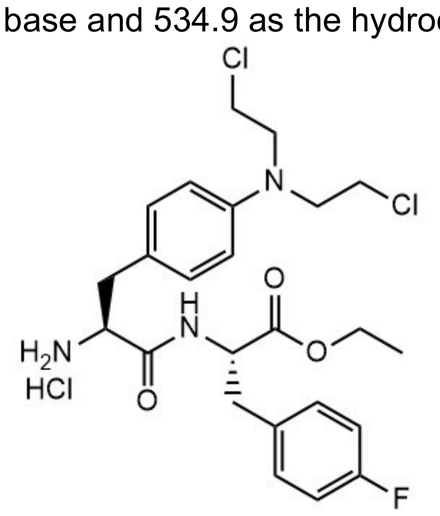
8.6 Renal Impairment

No dose adjustment of PEPAXTO is recommended in patients with creatinine clearance (CLcr) 45 to 89 mL/min calculated using Cockcroft-Gault equation *[see Clinical Pharmacology (12.3)]*. PEPAXTO has not been studied in patients with CLcr 15 to 44 mL/min.

11 DESCRIPTION

Melphalan flufenamide is an alkylating drug. The chemical name is Ethyl (2*S*)-2-[[(2*S*)-2-amino-3-[4-[bis(2-chloroethyl)amino]phenyl]propanoyl]amino]-3-(4-fluorophenyl)propanoate hydrochloride and the molecular weight is 498.4 as free base and 534.9 as the hydrochloride salt. The structural formula is:



Melphalan flufenamide hydrochloride is soluble in most organic solvents, while sparsely soluble in aqueous solutions. The pKa value is 7.13.

PEPAXTO for injection is supplied as a sterile, white to off-white lyophilized powder in a single-dose vial for intravenous use. Each vial contains 20 mg melphalan flufenamide (equivalent to 21.48 mg melphalan flufenamide hydrochloride) and 1,000 mg sucrose.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Melphalan flufenamide is a peptide conjugated alkylating drug. Due to its lipophilicity, melphalan flufenamide is passively distributed into cells and thereafter enzymatically hydrolyzed to melphalan. Similar to other nitrogen mustard drugs, cross-linking of DNA is involved in the antitumor activity of melphalan flufenamide. In cellular assays, melphalan flufenamide inhibited proliferation and induced apoptosis of hematopoietic and solid tumor cells. Additionally, melphalan flufenamide showed synergistic cytotoxicity with dexamethasone in melphalan resistant and non-resistant multiple myeloma cell lines.

12.2 Pharmacodynamics

The exposure-response relationship and time course of pharmacodynamic response for the safety and effectiveness of PEPAXTO have not been fully characterized.

Cardiac Electrophysiology

The effect of PEPAXTO on QT interval has not been fully characterized.

12.3 Pharmacokinetics

Melphalan flufenamide peak plasma concentrations were reached during the 30-minute infusion. Peak plasma concentrations of the active metabolite melphalan were reached 4 to 15 minutes after the end of infusion of PEPAXTO 40 mg. Following PEPAXTO 40 mg, the mean (CV%) C_{max} was 432 ng/mL (30%) and $AUC_{0\text{-}INF}$ was 3,143 µg/mL·hr (28%) for melphalan after a single dose. The mean (CV%) C_{max} was 419 ng/mL (33%) and $AUC_{0\text{-}INF}$ was 2,933 µg/mL·hr (29%) for melphalan at steady-state.

Distribution

In vivo the disappearance of melphalan flufenamide from plasma is rapid and is attributed to distribution to peripheral tissues with no late redistribution back to plasma.

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The mean (CV%) volume of distribution was 35 L (71%) for melphalan flufenamide and 76 L (32%) for melphalan after a single dose.

Elimination
After the end of infusion of PEPAXTO 40 mg, the mean (CV%) elimination half-life of melphalan flufenamide is 2.1 minutes (34%). The mean (CV%) elimination half-life of melphalan is 70 minutes (21%). The mean (CV%) clearance of melphalan flufenamide and melphalan is 692 L/hr (49%) and 23 L/hr (23%), respectively, at the recommended dosage of PEPAXTO 40 mg.

Metabolism
Melphalan flufenamide is metabolized in tissues to desethyl-melphalan flufenamide and melphalan. Melphalan is metabolized primarily by spontaneous hydrolysis to monohydroxy-melphalan and dihydroxy-melphalan.

Specific Populations
Higher melphalan exposures were observed in patients with lower body surface area. No clinically meaningful differences in the PK of melphalan were observed based on age (35 to 85 years old), renal impairment (CLcr 45 to 89 mL/min) and mild hepatic impairment (total bilirubin ≤ ULN and AST > ULN, or total bilirubin 1 to 1.5 × ULN and any AST).

The effect of sex, race/ethnicity, moderate to severe hepatic impairment (total bilirubin >1.5 × ULN and any AST), and renal impairment (CLcr 15 to 44 mL/min) on melphalan flufenamide and melphalan PK is unknown.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
No carcinogenicity studies have been conducted with melphalan flufenamide.

PEPAXTO is genotoxic. In studies conducted in vitro, melphalan flufenamide caused irreversible DNA damage. Repeat-dose toxicity studies with melphalan flufenamide in animals showed adverse effects on male reproductive organs. Melphalan flufenamide was administered intravenously to rats at 20, 40, or 55 mg/m^2, and to dogs at 0.45 or 0.90 mg/kg (9 or 18 mg/m^2) every 21 days for two or three doses. Decreased testes weights and depletion of germ cells were observed in both species, and epididymal oligospermia was observed in dogs. Adverse effects on male reproductive organs were observed in dogs at dose levels less than the recommended clinical dose of 40 mg. The reversibility of adverse effects on male reproductive organs was not assessed.

13.2 Animal Toxicology and/or Pharmacology
Dogs were intravenously administered a single dose of melphalan flufenamide (17.5 mg/kg) or an equimolar dose of melphalan; these dose levels were representative of dosages needed for myeloablation. Increased mortality was observed in dogs administered melphalan flufenamide despite similar melphalan exposure in animals administered melphalan flufenamide or melphalan.

14 CLINICAL STUDIES
The efficacy of PEPAXTO in combination with dexamethasone was evaluated in HORIZON [NCT02963493], a multicenter, single-arm trial. Eligible patients were required to have relapsed or refractory multiple myeloma. Patients received PEPAXTO 40 mg intravenously on Day 1 and dexamethasone 40 mg orally (20 mg for patients ≥75 years of age) on Day 1, 8, 15 and 22 of each 28-day cycle until disease progression or unacceptable toxicity.

A total of 157 patients accepting a central venous catheter and with estimated creatinine clearance by Cockcroft-Gaut formula ≥45 mL/min were enrolled. Patients with primary refractory disease (i.e. never responded with at least minimal response to any prior treatment) were excluded. Ninety seven patients had received four or more prior lines of therapies and were refractory to at least one proteasome inhibitor, at least one immunomodulatory agent and a CD38-directed monoclonal antibody. The median age was 65 years (range: 35 to 86 years); 58% were male, 87% were White and 6% were Black or African American. Disease characteristics in these 97 patients are summarized in Table 5.

The major efficacy outcome measure was overall response rate (ORR) and Duration of Response (DoR) assessed according to the International Myeloma Working Group (IMWG) Criteria by investigators. Efficacy results in the 97 patients are provided in Table 6. The median time to first response was 2.1 months (range: 1.0 to 6.1 months).

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Table 5: Disease Characteristics (HORIZON)

Parameter	**PEPAXTO with Dexamethasone (N=97)**
Years from diagnosis to start of PEPAXTO, median (range)	6.4 (2.1 to 24.6)
Prior treatment regimens, median (range)	6 (4 to 12)
Documented refractory status, (%)	
Lenalidomide	94
Pomalidomide	92
Bortezomib	74
Carfilzomib	63
Daratumumab	93
Alkylator refractory, (%)	75
Previous stem cell transplant, (%)	70
International Staging System at Baseline, (%)	
I	30
II	32
III	34
Missing/Unknown	4
High-risk cytogenetics[1], (%)	33
Extramedullary disease (EMD), (%)	41

[1] del(17p), t(4;14),t(14;16), gain (1q) and t(14;20) at study entry

Table 6: Efficacy Results (HORIZON)

	PEPAXTO with Dexamethasone (N=97)
Overall response rate (ORR), n (%) (95% CI)	23 (23.7) (15.7, 33.4)
Stringent complete response (sCR)	0
Complete Response (CR)	0
Very good partial response (VGPR), n (%)	9 (9.3)
Partial response (PR), n (%)	14 (14.4)
Median duration of response in months (95% CI)	4.2 (3.2, 7.6)

15 REFERENCES

1. “OSHA Hazardous Drugs.” OSHA. http://www.osha.gov/SLTC/hazardousdrugs/index.html

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

PEPAXTO is a white to off-white lyophilized powder for reconstitution (after reconstitution the solution is clear and colorless to light yellow) supplied in a 50 mL single dose vial containing 20 mg melphalan flufenamide. Each 20 mg vial is packaged in a single carton (NDC 73657-020-01).

The vial stopper is not manufactured with natural rubber latex.

Storage

Store refrigerated at 2°C to 8°C (36°F to 46°F) and protect from light. Retain in original carton until use.

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Handling and Disposal
PEPAXTO is a hazardous drug. Follow special handling and disposal procedures.[1] All materials that have been utilized for dilution and administration, including any reconstituted solution made over 30 minutes prior, should be disposed of according to standard procedures for hazardous drugs.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Thrombocytopenia, Neutropenia and Anemia
- Advise patients that PEPAXTO can cause myelosuppression. Advise patients to immediately report signs or symptoms of thrombocytopenia (bleeding and easy bruising), neutropenia (symptoms of infection, such as fever, chills, cough, pain, or burning during urination) and anemia (fatigue and shortness of breath) to their healthcare provider.
- Advise patients that complete blood counts will be monitored at baseline, during treatment, and as clinically indicated *[see Warnings and Precautions (5.1, 5.2, 5.3)].*

Infections
Advise patients that PEPAXTO can cause infections. Instruct patients to immediately report new or worsening signs or symptoms (e.g., chills, fever) of infection to their healthcare provider *[see Warnings and Precautions (5.4)].*

Secondary Malignancies
Advise patients on the risk of second primary malignancies *[see Warnings and Precautions (5.6)].*

Embryo-Fetal Toxicity
- Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.7) and Use in Specific Populations (8.1)].*
- Advise females of reproductive potential to use effective contraception during treatment with PEPAXTO and 6 months after the last dose *[see Use in Specific Populations (8.3)].*
- Advise males with female partners of reproductive potential to use effective contraception during treatment with PEPAXTO and for 3 months after the last dose *[see Use in Specific Populations (8.3)].*

Lactation
Advise women not to breastfeed during treatment with PEPAXTO and for 1 week after the last dose *[see Use in Specific Populations (8.2)].*

Manufactured for: Oncopeptides AB (publ), Stockholm, Sweden.

Distributed by: Oncopeptides Inc. 200 Fifth Avenue, Suite #1030 Waltham, MA 02451, USA

FULL PRESCRIBING INFORMATION: CONTENTS

PATIENT INFORMATION
PEPAXTO (peh-PAX-toe)
(melphalan flufenamide)
for injection, for intravenous use

What is PEPAXTO?

PEPAXTO is a prescription medicine used in combination with the medicine dexamethasone to treat adults with multiple myeloma who did not respond to or stopped responding to at least four prior medicines including at least one proteasome inhibitor, one immunomodulatory agent and one CD38-directed antibody.

PEPAXTO is not for use to prepare for transplant.

It is not known if PEPAXTO is safe and effective in children.

Do not receive PEPAXTO if you have a history of a severe allergic reaction to melphalan flufenamide or melphalan.

Before receiving PEPAXTO, tell your healthcare provider about all of your medical conditions, including if you:

- have an infection
- are pregnant or plan to become pregnant. PEPAXTO may harm your unborn baby.
  Females who are able to become pregnant:
  - Your healthcare provider will check to see if you are pregnant before you start treatment with PEPAXTO.
  - You should use an effective method of birth control (contraception) during treatment and for 6 months after the last dose of PEPAXTO.
  - Tell your healthcare provider right away if you become pregnant or think you may be pregnant during treatment with PEPAXTO.

  Males with female partners who are able to become pregnant:
  - You should use an effective method of birth control (contraception) during treatment and for 3 months after the last dose of PEPAXTO.
  - Talk to your healthcare provider about effective methods of birth control that you can use during this time.
- are breastfeeding or plan to breastfeed. It is not known if PEPAXTO passes into breast milk. Do not breastfeed during treatment with and for 1 week after the last dose of PEPAXTO.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How will I receive PEPAXTO?

- PEPAXTO is given to you by your healthcare provider into your vein through intravenous (IV) infusion over 30 minutes.
- PEPAXTO is usually given 1 time every 28 days.
- Your healthcare provider will decide how many treatments you need.
- Your healthcare provider will do blood tests before and during your treatment with PEPAXTO to check for side effects.
- Your healthcare provider may prescribe medicines to help prevent nausea before your infusion and during treatment with PEPAXTO.

What are the possible side effects of PEPAXTO?

PEPAXTO may cause serious side effects, including:

- **Low blood cell counts** are common with PEPAXTO and can be serious. Your healthcare provider will do blood tests as needed to check your blood cell counts during your treatment with PEPAXTO.
  - **Low platelet counts:** Tell your healthcare provider right away if you have a bleeding or bruising under the skin.
  - **Low red blood cell counts:** Tell your healthcare provider if you are feeling weak, tired or you get tired easily, you look pale, or if you feel short of breath.
  - **Low white blood cell counts**: A low white blood cell count increases the risk of infections.
- **Infections.** PEPAXTO can cause infections that have led to death. **Tell your healthcare provider right away if you develop new or worsening signs or symptoms of infection such as fever, chills, cough, pain, or burning during urination during treatment with PEPAXTO.**

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- **Secondary cancers**. New cancers such as myelodysplastic syndromes or acute leukemia have happened in people with multiple myeloma who have received PEPAXTO. Your healthcare provider will monitor you for new cancers.

Your healthcare provider may change your dose of PEPAXTO, stop your treatment for a period of time, or completely stop your treatment if you have certain side effects.

PEPAXTO may cause fertility problems in males and females, which may affect your ability to have children. Talk with your healthcare provider if you have concerns about fertility.

The most common side effects of PEPAXTO include, low blood cell counts, fatigue, nausea, diarrhea, fever, and cold-like symptoms (respiratory tract infection).

These are not all of the possible side effects of PEPAXTO.

Call your doctor for medical advice about side effects. You may report side effects to the FDA at 1-800-FDA-1088.

General information about the safe and effective use of PEPAXTO.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. You can ask your healthcare provider or pharmacist for information about PEPAXTO that is written for health professionals.

What are the ingredients in PEPAXTO?

Active ingredient: melphalan flufenamide

Inactive ingredient: sucrose

Manufactured for Oncopeptides AB (publ), Stockholm, Sweden.
Marketed and distributed by Oncopeptides Inc., 200 Fifth Avenue, Suite #1030 Waltham, MA 02451, USA.
PEPAXTO is a registered trademark of Oncopeptides AB (publ).
For more information, go to www.PEPAXTO.com or call 1-866-522-8894.

This Patient Information has been approved by the U.S. Food and Drug Administration. Issued: 02/2021

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Websites

Taiho Oncology, Inc. | Making the Human Connection
https://www.taihooncology.com/us/

Taiho Oncology Patient Support Website
https://www.taihooncology.com/us/

IMPORTANT INFORMATION FOR HEALTHCARE PROFESSIONALS

TAIHO ONCOLOGY PATIENT SUPPORT

A partner in your cancer care.

ONE TWO THREE ACCESS!

Helping you help your patients obtain access to Taiho Oncology medicines

CALL **1-844-TAIHO-4U** (1-844-824-4648)
FAX **1-844-287-2559**
VISIT **TaihoPatientSupport.com**

Access as easy as One, Two, Three

1 Three ways to enroll makes it convenient and easy for you:

BY FAX

Complete all applicable sections of a printed Patient Enrollment form, including patient and physician signatures, and fax the form to Taiho Oncology Patient Support at 1-844-287-2559

ONLINE

Complete the Patient Enrollment Form online at https://taihopatientsupport.com/how-to-enroll

BY PHONE

Call 1-844-TAIHO-4U (1-844-824-4648) for help with enrollment

2 HCPs can expect a Taiho Oncology Patient Support Reimbursement Specialist will:

- Contact you to confirm receipt of the Patient Enrollment Form and next steps
- Create the patient's account and ensure completeness of information
- Facilitate the services selected on the Patient Enrollment Form
- Be available to triage the patient's prescription and coordinate with the dispensing specialty pharmacy once coverage for the Taiho Oncology medicine has been verified
- Coordinate follow-up, reminders, and personalized nurse support upon request

3 Patients can expect:

- Taiho Oncology Patient Support will welcome the patient to the program and explains his or her insurance benefits for the prescribed Taiho Oncology medicine
- A Reimbursement Specialist will confirm patient access to the Taiho Oncology medicine or assist the patient in applying for financial assistance to help cover the cost of the Taiho Oncology medicine
- The specialty pharmacy will call the patient to discuss payment and shipment, if applicable
- The patient receives the prescribed Taiho Oncology medicine from the specialty pharmacy, physician, or hospital and has instructions for use to begin treatment

Meeting the access needs of your patients

We know that getting patients access to their medicine is an important step. We strive to make this process as simple as possible.

We are here to assist with:

Insurance Coverage Support

- Benefits verification to determine coverage for the patient's Taiho Oncology medicine and help explaining those benefits to the patient
- Prior authorization assistance to meet payer requirements
- Appeals assistance for denied prior authorizations

Specialty Pharmacy Prescription Coordination

We will triage the patient's prescription; coordinate with the in-network specialty pharmacy, self-dispensing practice, or hospital outpatient pharmacy, and communicate with the patient about his or her prescription status.

Personalized Nurse Support

Our nurse support services are available as needed to support patient care, including education about the importance of taking the medicine as prescribed and refill reminders.

CALL **1-844-TAIHO-4U** (1-844-824-4648)
FAX **1-844-287-2559**
VISIT **TaihoPatientSupport.com**

TAIHO ONCOLOGY

Financial assistance for your patients

TYPE OF PATIENT COVERAGE:		HOW WE CAN HELP:
	**Privately/commercially insured patients**	**Taiho Oncology Patient Support Co-pay Program** Eligible, privately insured patients can enroll in the Taiho Oncology Patient Support Co-pay Program to reduce out-of-pocket expenses to $0 for their Taiho Oncology medicine https://www.taihooncologycopay.com/
	**Publicly/government-insured patients** **OR**	**Alternate Funding Support** We research financial assistance opportunities for patients with insufficient prescription insurance coverage or insufficient resources to pay for their Taiho Oncology medicine. We refer those patients to nonprofit foundations for co-pay or other financial assistance. Programs include: **Medicare Part D Extra Help:** Extra Help is a Medicare program designed to help patients with limited income and resources. Those who qualify for the Extra Help program and who join a Medicare drug plan receive help with paying their Medicare drug plan's costs and incur no late enrollment penalty. https://secure.ssa.gov/i1020/start
	**Underinsured or uninsured patients**	**Patient Assistance Program** Taiho Oncology provides financial assistance for eligible patients who have insufficient insurance coverage for their Taiho Oncology medicine, including Medicaid, Medicare, or any other public or private program, and who have insufficient financial resources to pay for their treatment. To apply, the patient will need to read, fill out, and sign page 3 of the Patient Enrollment Form. Income documentation and insurance information will be required. Taiho Oncology Patient Support may arrange for the patient to receive their prescribed Taiho Oncology medicine at no cost based on assistance, financial, and medical criteria.

CALL **1-844-TAIHO-4U** (1-844-824-4648)
FAX **1-844-287-2559**
VISIT **TaihoPatientSupport.com**

*Taiho Oncology does not influence or control the decisions of these co-pay assistance foundations, but Taiho Oncology Patient Support can assist patients by making an appropriate referral based on a patient's diagnosis and by assisting with the application process. Each co-pay assistance foundation has its own criteria for patient eligibility. We cannot guarantee financial assistance once a patient has been referred.

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INQOVI® (decitabine and cedazuridine) tablets—the first and only oral hypomethylating agent (HMA) for the treatment of myelodysplastic syndromes (MDS), including CMML. With INQOVI, patients can take their therapy in the convenience and comfort of their own home.

CMML=chronic myelomonocytic leukemia.

INDICATIONS

INQOVI is indicated for treatment of adult patients with myelodysplastic syndromes (MDS), including previously treated and untreated, de novo and secondary MDS with the following French-American-British subtypes (refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, and chronic myelomonocytic leukemia [CMML]) and intermediate-1, intermediate-2, and high-risk International Prognostic Scoring System groups.

SELECTED IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Myelosuppression

Fatal and serious myelosuppression can occur with INQOVI. Based on laboratory values, new or worsening thrombocytopenia occurred in 82% of patients, with Grade 3 or 4 occurring in 76%. Neutropenia occurred in 73% of patients, with Grade 3 or 4 occurring in 71%. Anemia occurred in 71% of patients, with Grade 3 or 4 occurring in 55%. Febrile neutropenia occurred in 33% of patients, with Grade 3 or 4 occurring in 32%. Myelosuppression (thrombocytopenia, neutropenia, anemia, and febrile neutropenia) is the most frequent cause of INQOVI dose reduction or interruption, occurring in 36% of patients. Permanent discontinuation due to myelosuppression (febrile neutropenia) occurred in 1% of patients. Myelosuppression and worsening neutropenia may occur more frequently in the first or second treatment cycles and may not necessarily indicate progression of underlying MDS.

Please see additional Important Safety Information on back cover and full Prescribing Information in pocket or at INQOVI.com/PI.

INQOVI®
(decitabine and cedazuridine)
35mg / 100mg tablets

The only oral HMA for MDS, including CMML, that

Patients can take from the comfort of home

Oral dosing

INQOVI® (decitabine and cedazuridine) tablets are a fixed-dose combination tablet containing decitabine (35 mg) and cedazuridine (100 mg), a cytidine deaminase inhibitor that enhances oral bioavailability of decitabine and also increases its systemic exposure.

INQOVI should be taken once a day at approximately the same time on days 1 through 5 of each 28-day cycle for a minimum of 4 cycles. A complete or partial response may take longer than 4 cycles.

Tablet shown is not actual size. Actual tablet size is 7.94 mm x 14.29 mm.

28-day dosing cycle

Week 1	Take 1 tablet once daily for 5 days	2 days rest
Week 2	Rest	
Week 3	Rest	
Week 4	Rest	

- Patients should avoid eating for 2 hours before and 2 hours after taking INQOVI
- Tablets must be swallowed whole—not cut, crushed, or chewed
- Consider administering antiemetics prior to each dose to minimize nausea and vomiting
- Do NOT substitute INQOVI for an intravenous (IV) decitabine product within a cycle
- Patients should take INQOVI at the same time each day

DosePak is 7.35 in x 2.45 in.

ASCERTAIN PHASE 3 CROSSOVER TRIAL (N=133)

Study design
INQOVI was studied in a phase 3 crossover trial designed to assess systemic decitabine exposure, demethylation activity, and safety between IV decitabine and INQOVI. The primary endpoint was 5-day area under the curve between INQOVI and IV decitabine.

SELECTED IMPORTANT SAFETY INFORMATION

Fatal and serious infectious complications can occur with INQOVI. Pneumonia occurred in 21% of patients, with Grade 3 or 4 occurring in 15%. Sepsis occurred in 14% of patients, with Grade 3 or 4 occurring in 11%. Fatal pneumonia occurred in 1% of patients, fatal sepsis in 1%, and fatal septic shock in 1%.

Proven efficacy results in ASCERTAIN phase 3 crossover trial

Primary endpoint results

Orally administered INQOVI demonstrated equivalent systemic exposure to IV-administered decitabine

99% **ratio of oral to IV 5-day decitabine AUC**
(90% CI: 93, 106)

- This ratio is the geometric mean of the 5-day cumulative decitabine AUC between INQOVI and IV-administered decitabine when administered once daily for 5 consecutive days

Efficacy results in patients with MDS or CMML in phase 3 crossover trial (N=133)

21% OF PATIENTS
achieved a complete response
(CR, 95% CI: 15, 29)

7.5 MONTHS
median duration of CR*
(range: 1.6-17.5)

4.3 MONTHS
median time to CR
(range: 2.1-15.2)

Transfusion dependence

53% **of the patients treated with INQOVI who were initially transfusion dependent achieved posttreatment RBC and platelet transfusion independence (30/57)†**

63% **of patients who initially were both RBC and platelet transfusion independent remained transfusion independent (48/76)†**

Safety results similar to IV decitabine

The most common adverse reactions (≥ 20%) were fatigue (55%), constipation (44%), hemorrhage (43%), myalgia (42%), mucositis (41%), arthralgia (40%), nausea (40%), dyspnea (38%), diarrhea (37%), rash (33%), dizziness (33%), febrile neutropenia (33%), edema (30%), headache (30%), cough (28%), decreased appetite (24%), upper respiratory tract infection (23%), pneumonia (21%), and transaminase increased (21%). The most common Grade 3 or 4 laboratory abnormalities (≥ 50%) were leukocytes decreased (81%), platelet count decreased (76%), neutrophil count decreased (71%), and hemoglobin decreased (55%).

- Incidence of cytopenias was slightly higher in INQOVI during cycle 1 compared to IV decitabine
- These are not the only adverse reactions or laboratory abnormalities seen with INQOVI. Please see full Prescribing Information for complete safety profile

AUC=area under the curve; CI=confidence interval; RBC=red blood cell.
*From start of CR until relapse or death.
†During any consecutive 56-day postbaseline period.

Please see additional Important Safety Information on back cover and full Prescribing Information in pocket or at INQOVI.com/PI.

INQOVI®
(decitabine and cedazuridine)
35mg / 100mg tablets

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Myelosuppression

Fatal and serious myelosuppression can occur with INQOVI. Based on laboratory values, new or worsening thrombocytopenia occurred in 82% of patients, with Grade 3 or 4 occurring in 76%. Neutropenia occurred in 73% of patients, with Grade 3 or 4 occurring in 71%. Anemia occurred in 71% of patients, with Grade 3 or 4 occurring in 55%. Febrile neutropenia occurred in 33% of patients, with Grade 3 or 4 occurring in 32%. Myelosuppression (thrombocytopenia, neutropenia, anemia, and febrile neutropenia) is the most frequent cause of INQOVI dose reduction or interruption, occurring in 36% of patients. Permanent discontinuation due to myelosuppression (febrile neutropenia) occurred in 1% of patients. Myelosuppression and worsening neutropenia may occur more frequently in the first or second treatment cycles and may not necessarily indicate progression of underlying MDS.

Fatal and serious infectious complications can occur with INQOVI. Pneumonia occurred in 21% of patients, with Grade 3 or 4 occurring in 15%. Sepsis occurred in 14% of patients, with Grade 3 or 4 occurring in 11%. Fatal pneumonia occurred in 1% of patients, fatal sepsis in 1%, and fatal septic shock in 1%.

Obtain complete blood cell counts prior to initiation of INQOVI, prior to each cycle, and as clinically indicated to monitor response and toxicity. Administer growth factors and anti-infective therapies for treatment or prophylaxis as appropriate. Delay the next cycle and resume at the same or reduced dose as recommended.

Embryo-Fetal Toxicity

INQOVI can cause fetal harm. Advise pregnant women of the potential risk to a fetus. Advise patients to use effective contraception during treatment and for 6 months (females) or 3 months (males) after last dose.

ADVERSE REACTIONS

Serious adverse reactions in > 5% of patients included febrile neutropenia (30%), pneumonia (14%), and sepsis (13%). Fatal adverse reactions included sepsis (1%), septic shock (1%), pneumonia (1%), respiratory failure (1%), and one case each of cerebral hemorrhage and sudden death.

The most common adverse reactions (≥ 20%) were fatigue (55%), constipation (44%), hemorrhage (43%), myalgia (42%), mucositis (41%), arthralgia (40%), nausea (40%), dyspnea (38%), diarrhea (37%), rash (33%), dizziness (33%), febrile neutropenia (33%), edema (30%), headache (30%), cough (28%), decreased appetite (24%), upper respiratory tract infection (23%), pneumonia (21%), and transaminase increased (21%). The most common Grade 3 or 4 laboratory abnormalities (≥ 50%) were leukocytes decreased (81%), platelet count decreased (76%), neutrophil count decreased (71%), and hemoglobin decreased (55%).

USE IN SPECIFIC POPULATIONS

Lactation

Because of the potential for serious adverse reactions in the breastfed child, advise women not to breastfeed during treatment with INQOVI and for at least 2 weeks after the last dose.

Renal Impairment

No dosage modification of INQOVI is recommended for patients with mild or moderate renal impairment (creatinine clearance [CLcr] of 30 to 89 mL/min based on Cockcroft-Gault). Due to the potential for increased adverse reactions, monitor patients with moderate renal impairment (CLcr 30 to 59 mL/min) frequently for adverse reactions. INQOVI has not been studied in patients with severe renal impairment (CLcr 15 to 29 mL/min) or end-stage renal disease (ESRD: CLcr <15 mL/min).

Please see full Prescribing Information in pocket or at INQOVI.com/PI.

Reference: INQOVI [package insert]. Princeton, NJ: Taiho Oncology, Inc.; 2020.

TAIHO ONCOLOGY

 11/2020 INQ-PM-US-0191

INQOVI®
(decitabine and cedazuridine)
35mg / 100mg tablets

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use INQOVI safely and effectively. See full prescribing information for INQOVI.

INQOVI® (decitabine and cedazuridine) tablets, for oral use
Initial U.S. Approval: 2020

INDICATIONS AND USAGE

INQOVI is a combination of decitabine, a nucleoside metabolic inhibitor, and cedazuridine, a cytidine deaminase inhibitor, indicated for treatment of adult patients with myelodysplastic syndromes (MDS), including previously treated and untreated, de novo and secondary MDS with the following French-American-British subtypes (refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, and chronic myelomonocytic leukemia [CMML]) and intermediate-1, intermediate-2, and high-risk International Prognostic Scoring System groups. (1)

DOSAGE AND ADMINISTRATION

- The recommended dosage of INQOVI is 1 tablet (35 mg decitabine and 100 mg cedazuridine) taken orally once daily on Days 1 through 5 of each 28-day cycle. (2.2)
- Take INQOVI on an empty stomach. (2.2)

DOSAGE FORMS AND STRENGTHS

Tablets: 35 mg decitabine and 100 mg cedazuridine. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Myelosuppression: Fatal and serious myelosuppression and infectious complications can occur. Obtain complete blood cell counts prior to initiation of INQOVI, prior to each cycle, and as clinically indicated to monitor for response and toxicity. Delay the next cycle and resume at the same or reduced dose as recommended. (2.3, 5.1)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise patients of reproductive potential of the potential risk to a fetus and to use effective contraception. (5.2, 8.1, 8.3)

ADVERSE REACTIONS

Most common adverse reactions (incidence ≥ 20%) are fatigue, constipation, hemorrhage, myalgia, mucositis, arthralgia, nausea, dyspnea, diarrhea, rash, dizziness, febrile neutropenia, edema, headache, cough, decreased appetite, upper respiratory tract infection, pneumonia, and transaminase increased. The most common Grade 3 or 4 laboratory abnormalities (≥ 50%) were leukocytes decreased, platelet count decreased, neutrophil count decreased, and hemoglobin decreased. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Taiho Oncology, Inc. at 1-844-878-2446 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Drugs Metabolized by Cytidine Deaminase: Avoid coadministration with INQOVI. (7)

USE IN SPECIFIC POPULATIONS

- Lactation: Advise not to breastfeed. (8.2)
- Infertility: Can impair fertility. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 07/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

INQOVI is indicated for treatment of adult patients with myelodysplastic syndromes (MDS), including previously treated and untreated, de novo and secondary MDS with the following French-American-British subtypes (refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, and chronic myelomonocytic leukemia [CMML]) and intermediate-1, intermediate-2, and high-risk International Prognostic Scoring System groups.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Information

Do NOT substitute INQOVI for an intravenous decitabine product within a cycle.

Consider administering antiemetics prior to each dose to minimize nausea and vomiting *[see Adverse Reactions (6.1)]*.

2.2 Recommended Dosage

The recommended dosage of INQOVI is 1 tablet (containing 35 mg decitabine and 100 mg cedazuridine) orally once daily on Days 1 through 5 of each 28-day cycle for a minimum of 4 cycles until disease progression or unacceptable toxicity. A complete or partial response may take longer than 4 cycles.

Instruct patients of the following:

- Take INQOVI at the same time each day.
- Swallow tablets whole. Do not cut, crush, or chew tablets.
- Do not consume food 2 hours before and 2 hours after each dose.
- Take one tablet a day for 5 days in each cycle. If the patient misses a dose within 12 hours of the time it is usually taken, instruct patients to take the missed dose as soon as possible and then to resume the normal daily dosing schedule. Extend the dosing period by one day for every missed dose to complete 5 daily doses for each cycle.
- Do not take an additional dose if vomiting occurs after INQOVI administration but continue with the next schedule dose.

INQOVI is a hazardous drug. Follow applicable special handling and disposal procedures.[1]

2.3 Monitoring and Dosage Modifications for Adverse Reactions

Hematologic Adverse Reactions

Obtain complete blood cell counts prior to initiating INQOVI and before each cycle. Delay the next cycle if absolute neutrophil count (ANC) is less than 1,000/µL and platelets are less than 50,000/µL in the

absence of active disease. Monitor complete blood cell counts until ANC is 1,000/µL or greater and platelets are 50,000/µL or greater *[see Warnings and Precautions (5.1)]*.

- If hematologic recovery occurs (ANC at least 1,000/µL and platelets at least 50,000/µL) within 2 weeks of achieving remission, continue INQOVI at the same dose.
- If hematologic recovery does not occur (ANC at least 1,000/µL and platelets at least 50,000/µL) within 2 weeks of achieving remission,
  - Delay INQOVI for up to 2 additional weeks AND
  - Resume at a reduced dose by administering INQOVI on Days 1 through 4. Consider further dose reductions in the order listed in Table 1 if myelosuppression persists after a dose reduction. Maintain or increase dose in subsequent cycles as clinically indicated.

Table 1: Recommended INQOVI Dose Reductions for Myelosuppression

Dose Reduction	**Dosage**
First	1 tablet orally once daily on Days 1 through 4
Second	1 tablet orally once daily on Days 1 through 3
Third	1 tablet orally once daily on Days 1, 3 and 5

Manage persistent severe neutropenia and febrile neutropenia with supportive treatment *[see Warnings and Precautions (5.1)]*.

Non-Hematologic Adverse Reactions

Delay the next cycle for the following non-hematologic adverse reactions and resume at the same or reduced dose upon resolution:

- Serum creatinine 2 mg/dL or greater
- Serum bilirubin 2 times upper limit of normal (ULN) or greater
- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) 2 times ULN or greater
- Active or uncontrolled infection

3 DOSAGE FORMS AND STRENGTHS

INQOVI tablets contain 35 mg decitabine and 100 mg cedazuridine. The tablets are biconvex, oval-shaped, film-coated, red and debossed with “H35” on one side.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Myelosuppression

Fatal and serious myelosuppression can occur with INQOVI. Based on laboratory values, new or worsening thrombocytopenia occurred in 82% of patients, with Grade 3 or 4 occurring in 76%. Neutropenia occurred in 73% of patients, with Grade 3 or 4 occurring in 71%. Anemia occurred in 71% of patients, with Grade 3 or 4 occurring in 55%. Febrile neutropenia occurred in 33% of patients, with Grade 3 or 4 occurring in 32%. Myelosuppression (thrombocytopenia, neutropenia, anemia, and febrile neutropenia) is the most frequent cause of INQOVI dose reduction or interruption, occurring in 36% of patients. Permanent discontinuation due to myelosuppression (febrile neutropenia) occurred in 1% of patients. Myelosuppression and worsening neutropenia may occur more frequently in the first or second treatment cycles and may not necessarily indicate progression of underlying MDS.

Fatal and serious infectious complications can occur with INQOVI. Pneumonia occurred in 21% of patients, with Grade 3 or 4 occurring in 15%. Sepsis occurred in 14% of patients, with Grade 3 or 4 occurring in 11%. Fatal pneumonia occurred in 1% of patients, fatal sepsis in 1%, and fatal septic shock in 1% *[see Adverse Reactions (6.1)]*.

Obtain complete blood cell counts prior to initiation of INQOVI, prior to each cycle, and as clinically indicated to monitor response and toxicity. Administer growth factors and anti-infective therapies for treatment or prophylaxis as appropriate. Delay the next cycle and resume at the same or reduced dose as recommended *[see Dosage and Administration (2.3)]*.

5.2 Embryo-Fetal Toxicity

Based on findings from human data, animal studies, and its mechanism of action, INQOVI can cause fetal harm when administered to a pregnant woman. In nonclinical studies with decitabine in mice and rats, decitabine was teratogenic, fetotoxic, and embryotoxic at doses less than the recommended human dose.

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with INQOVI and for 6 months after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with INQOVI and for 3 months after the last dose *[see Use in Specific Populations (8.1, 8.3)]*.

6 ADVERSE REACTIONS

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

- Myelosuppression *[see Warnings and Precautions (5.1)]*

6.1 Clinical Trials Experience

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

Myelodysplastic Syndrome and Chronic Myelomonocytic Leukemia

The safety of INQOVI was evaluated in a pooled safety population that includes patients enrolled in Study ASTX727-01-B and Study ASTX727-02 *[see Clinical Studies (14)]*.

Patients were randomized to receive INQOVI (35 mg decitabine and 100 mg cedazuridine) orally once daily on Days 1 through 5 in Cycle 1 and decitabine 20 mg/m^2 intravenously on Days 1 through 5 in Cycle 2, or the reverse sequence, and then INQOVI (35 mg decitabine and 100 mg cedazuridine) orally once daily on Days 1 through 5 of each 28-day cycle in Cycles 3 and beyond. Patients were allowed to have one prior cycle of decitabine or azacitidine and there was no limit for body weight or surface area. Among the patients who received INQOVI, 61% of patients were exposed for 6 months or longer and 24% were exposed to INQOVI for greater than 1 year.

Serious adverse reactions occurred in 68% of patients who received INQOVI. Serious adverse reactions in > 5% of patients included febrile neutropenia (30%), pneumonia (14%), and sepsis (13%). Fatal adverse reactions occurred in 6% of patients. These included sepsis (1%), septic shock (1%), pneumonia (1%), respiratory failure (1%), and one case each of cerebral hemorrhage and sudden death.

Permanent discontinuation due to an adverse reaction occurred in 5% of patients who received INQOVI. The most frequent adverse reactions resulting in permanent discontinuation were febrile neutropenia (1%) and pneumonia (1%).

Dose interruptions due to an adverse reaction occurred in 41% of patients who received INQOVI. Adverse reactions requiring dosage interruptions in > 5% of patients who received INQOVI included neutropenia (18%), febrile neutropenia (8%), thrombocytopenia (6%), and anemia (5%).

Dose reductions due to an adverse reaction occurred in 19% of patients who received INQOVI. Adverse reactions requiring dosage reductions in > 2% of patients who received INQOVI included neutropenia (12%), anemia (3%), and thrombocytopenia (3%).

The most common adverse reactions (≥ 20%) were fatigue, constipation, hemorrhage, myalgia, mucositis, arthralgia, nausea, dyspnea, diarrhea, rash, dizziness, febrile neutropenia, edema, headache, cough, decreased appetite, upper respiratory tract infection, pneumonia, and transaminase increased. The most common Grade 3 or 4 laboratory abnormalities (≥ 50%) were leukocytes decreased, platelet count decreased, neutrophil count decreased, and hemoglobin decreased.

Table 2 summarizes the adverse reactions in the pooled safety population.

Table 2: Adverse Reactions (≥ 10%) in Patients Who Received INQOVI in Pooled Safety Population

Adverse Reactions	INQOVI Cycle 1 N=107		Intravenous Decitabine Cycle 1 N=106		INQOVI† All Cycles N=208	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
General disorders and administration site conditions						
Fatigue[1]	29	2	25	0	55	5
Hemorrhage[2]	24	2	17	0	43	3
Edema[3]	10	0	11	0	30	0.5
Pyrexia	7	0	7	0	19	1
Gastrointestinal disorders						
Constipation[4]	20	0	23	0	44	0
Mucositis[5]	18	1	24	2	41	4
Nausea	25	0	16	0	40	0.5
Diarrhea[6]	16	0	11	0	37	1
Transaminase increased[7]	12	1	3	0	21	3
Abdominal pain[8]	9	0	7	0	19	1
Vomiting	5	0	5	0	15	0
Musculoskeletal and connective tissue disorders						
Myalgia[9]	9	2	16	1	42	3
Arthralgia[10]	9	1	13	1	40	3
Respiratory, thoracic, and mediastinal disorders						
Dyspnea[11]	17	3	9	3	38	6
Cough[12]	7	0	8	0	28	0
Blood & lymphatic system disorders						
Febrile neutropenia	10	10	13	13	33	32
Skin and subcutaneous tissue disorders						
Rash[13]	12	1	11	1	33	0.5

Adverse Reactions	INQOVI Cycle 1 N=107		Intravenous Decitabine Cycle 1 N=106		INQOVI† All Cycles N=208	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Nervous system disorders						
Dizziness[14]	16	1	11	0	33	2
Headache[15]	22	0	13	0	30	0
Neuropathy[16]	4	0	8	0	13	0
Metabolism and nutritional disorders						
Decreased appetite	10	1	6	0	24	2
Infections and infestations						
Upper respiratory tract infection[17]	6	0	3	0	23	1
Pneumonia[18]	7	7	7	5	21	15
Sepsis[19]	6	6	2	1	14	11
Cellulitis[20]	4	1	3	2	12	5
Investigations						
Renal impairment[21]	9	0	8	1	18	0
Weight decreased	5	0	3	0	10	1
Injury, poisoning, and procedural complications						
Fall	4	0	1	0	12	1
Psychiatric disorders						
Insomnia	6	0	2	0	12	0.5
Vascular disorders						
Hypotension[22]	4	0	6	1	11	2
Cardiac Disorders						
Arrhythmia[23]	3	0	2	0	11	1

†Includes adverse reactions that occurred during all cycles, including during treatment with 1 cycle of intravenous decitabine.

1 Includes fatigue, asthenia, and lethargy

2 Includes contusion, epistaxis, petechiae, hematuria, conjunctival hemorrhage, mouth hemorrhage, purpura, angina bullosa hemorrhagica, gingival bleeding, hematoma, hemoptysis, eye contusion, hemorrhagic diathesis, increased tendency to bruise, vaginal hemorrhage, abdominal wall hematoma, blood blister, bone contusion, catheter site bruise, ecchymosis, genital hemorrhage, intra-

Adverse Reactions	INQOVI Cycle 1 N=107		Intravenous Decitabine Cycle 1 N=106		INQOVI† All Cycles N=208	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)

abdominal hematoma, oral mucosa hematoma, periorbital hemorrhage, procedural hemorrhage, pulmonary alveolar hemorrhage, retinal hemorrhage, scleral hemorrhage, thrombotic thrombocytopenic purpura, tongue hemorrhage, and vessel puncture site hemorrhage

[3] Includes edema peripheral, peripheral swelling, swelling face, fluid overload, localized edema, face edema, edema, eye swelling, eyelid edema, fluid retention, periorbital swelling, scrotal edema, scrotal swelling, and swelling

[4] Includes constipation and feces hard

[5] Includes oropharyngeal pain, stomatitis, mouth ulceration, proctalgia, oral pain, gingivitis, oral disorder, gingival pain, colitis, glossodynia, mouth swelling, pharyngitis, proctitis, duodenitis, enteritis, gingival discomfort, gingival swelling, lip disorder, lip ulceration, mucosal ulceration, nasal ulcer, noninfective gingivitis, oral mucosal blistering, oral mucosal erythema, pharyngeal erythema, pharyngeal ulceration, tongue ulceration, and vulvitis

[6] Includes diarrhea and feces soft

[7] Includes alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, gamma-glutamyltransferase increased, liver function test increased, and transaminases increased

[8] Includes abdominal pain, abdominal pain upper, abdominal pain lower, epigastric discomfort, and abdominal discomfort

[9] Includes myalgia, pain in extremity, muscle spasms, pain, musculoskeletal pain, non-cardiac chest pain, muscular weakness, musculoskeletal chest pain, flank pain, musculoskeletal stiffness, muscle strain, and musculoskeletal discomfort

[10] Includes arthralgia, back pain, neck pain, joint stiffness, pain in jaw, joint swelling, bursitis, joint range of motion decreased, and joint injury

[11] Includes dyspnea, dyspnea exertional, hypoxia, wheezing, chronic obstructive pulmonary disease, and tachypnoea

[12] Includes cough and productive cough

[13] Includes maculo-papular rash, rash, erythema, skin lesion, folliculitis, dermatitis, dermatitis acneiform, eczema, erythema multiforme, rash erythematous, seborrheic keratosis, skin ulcer, dermatitis allergic, dermatitis contact, eczema nummular, genital erythema, rash papular, rash pruritic, rash pustular, seborrheic dermatitis, skin exfoliation, skin irritation, stasis dermatitis, and ulcerative keratitis

[14] Includes dizziness, vertigo, postural dizziness, and positional vertigo

[15] Includes headache, sinus pain, and sinus headache

[16] Includes hypoesthesia, paresthesia, neuropathy peripheral, gait disturbance, peripheral sensory neuropathy, ataxia, balance disorder, brachial plexopathy, carpal tunnel syndrome, and radicular pain

[17] Includes upper respiratory tract infection, nasopharyngitis, sinusitis, and viral upper respiratory tract infection

[18] Includes pneumonia, pneumonitis, atypical pneumonia, and lung infection

[19] Includes sepsis, bacteremia, septic shock, endocarditis, pseudomonal bacteremia, and staphylococcal bacteremia

[20] Includes cellulitis, catheter site cellulitis, and infected bite

[21] Includes blood creatinine increased, acute kidney injury, blood urea increased, blood creatine increased, and renal failure

[22] Includes hypotension, blood pressure decreased, and cardiogenic shock

[23] Includes sinus tachycardia, atrial fibrillation, bradycardia, tachycardia, atrial flutter, sinus bradycardia, and conduction disorder

Clinically relevant adverse reactions in < 10% of patients who received INQOVI included:

- Acute febrile neutrophilic dermatosis (Sweet's syndrome) (1%)
- Tumor lysis syndrome (0.5%)

Table 3: Select Laboratory Abnormalities (> 20%) Worsening from Baseline in Patients Who Received INQOVI in Pooled Safety Population

Lab Abnormality*	INQOVI Cycle 1†		Intravenous Decitabine Cycle 1†		INQOVI All Cycles†	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Hematology						
Leukocytes decreased	79	65	77	59	87	81
Platelet count decreased	79	65	77	67	82	76
Neutrophil count decreased	70	65	62	59	73	71
Hemoglobin decreased	58	41	59	36	71	55
Chemistry						
Glucose increased	19	0	11	0	54	7
Albumin decreased	22	1	20	0	45	2
Alkaline phosphatase increased	22	1	12	0	42	0.5
Glucose decreased	14	0	17	0	40	1
Alanine aminotransferase increased	13	1	7	0	37	2
Sodium decreased	9	2	8	0	30	4
Calcium decreased	16	0	12	0	30	2
Aspartate aminotransferase increased	6	1	2	0	30	2
Creatinine increased	7	0	8	0	29	0.5

* Includes any lab abnormalities that worsened by one or more grades. Grade 3-4 includes any lab abnormalities that worsened to Grade 3 or Grade 4.

† The denominator used to calculate the rate varied from 103 to 107 for INQOVI Cycle 1, from 102 to 106 for Intravenous Decitabine Cycle and from 203 to 208 for INQOVI All Cycles based on the number of patients with a baseline value and at least one post-treatment value.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of intravenous decitabine. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and Lymphatic System Disorders: Differentiation syndrome

Respiratory, Thoracic and Mediastinal Disorders: Interstitial lung disease

7 DRUG INTERACTIONS

7.1 Effects of INQOVI on Other Drugs

Drugs Metabolized by Cytidine Deaminase

Cedazuridine is an inhibitor of the cytidine deaminase (CDA) enzyme. Coadministration of INQOVI with drugs that are metabolized by CDA may result in increased systemic exposure with potential for increased toxicity of these drugs *[see Clinical Pharmacology (12.3)]*. Avoid coadministration of INQOVI with drugs that are metabolized by CDA.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from human data, animal studies, and its mechanism of action *[see Clinical Pharmacology (12.1)]*, INQOVI can cause fetal harm when administered to a pregnant woman. A single published case report of intravenous decitabine use throughout the first trimester during pregnancy describes adverse developmental outcomes, including major birth defects (structural abnormalities). In animal reproduction studies, intravenous administration of decitabine to pregnant mice and rats during organogenesis at doses approximately 7% of the recommended human dose on a body surface area (mg/m^2) basis caused adverse developmental outcomes, including increased embryo-fetal mortality, alterations to growth, and structural abnormalities *(see Data)*. Advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Human Data

There are no available data on INQOVI use in pregnant women.

A single published case report of intravenous decitabine pregnancy exposure in a 39-year-old woman with a hematologic malignancy described multiple structural abnormalities after 6 cycles of therapy in the 18^{th} week of gestation. These abnormalities included holoprosencephaly, absence of nasal bone, mid-facial deformity, cleft lip and palate, polydactyly, and rocker-bottom feet. The pregnancy was terminated.

Animal Data

No reproductive or developmental toxicity studies have been conducted with INQOVI or cedazuridine.

In utero exposure to decitabine causes temporal-related defects in the rat and/or mouse, which include growth suppression, exencephaly, defective skull bones, rib/sternabrae defects, phocomelia, digit defects, micrognathia, gastroschisis, and micromelia. Decitabine inhibits proliferation and increases apoptosis of neural progenitor cells of the fetal central nervous system (CNS) and induces palatal clefting in the developing murine fetus. Studies in mice have also shown that decitabine administration during osteoblastogenesis (Day 10 of gestation) induces bone loss in offspring.

In mice exposed to single intraperitoneal decitabine injections (0, 0.9 and 3.0 mg/m^2, approximately 2% and 7% of the recommended daily clinical dose, respectively) over gestation Days 8, 9, 10 or 11, no maternal toxicity was observed, but reduced fetal survival was observed after treatment at 3 mg/m^2 and decreased fetal weight was observed at both dose levels. The 3 mg/m^2 dose elicited characteristic fetal defects for each treatment day, including supernumerary ribs (both dose levels), fused vertebrae and ribs, cleft palate, vertebral defects, hind-limb defects, and digital defects of fore- and hind-limbs.

In rats given a single intraperitoneal injection of 2.4, 3.6 or 6 mg/m^2 decitabine (approximately 5, 8, or 13% the daily recommended clinical dose, respectively) on gestation Days 9-12, no maternal toxicity was observed. No live fetuses were seen at any dose when decitabine was injected on gestation Day 9. A significant decrease in fetal survival and reduced fetal weight at doses greater than 3.6 mg/m^2 was seen when decitabine was given on gestation Day 10. Increased incidences of vertebral and rib anomalies were seen at all dose levels, and induction of exophthalmia, exencephaly, and cleft palate were observed at 6.0 mg/m^2. Increased incidence of foredigit defects was seen in fetuses at doses greater than 3.6 mg/m^2. Reduced size and ossification of long bones of the fore-limb and hind-limb were noted at 6 mg/m^2.

The effect of decitabine on postnatal development and reproductive capacity was evaluated in mice administered a single 3 mg/m^2 intraperitoneal injection (approximately 7% the recommended daily clinical dose) on Day 10 of gestation. Body weights of males and females exposed in utero to decitabine were significantly reduced relative to controls at all postnatal time points. No consistent effect on fertility was seen when female mice exposed in utero were mated to untreated males. Untreated females mated to males exposed in utero showed decreased fertility at 3 and 5 months of age (36% and 0% pregnancy rate, respectively). Follow up studies indicated that treatment of pregnant mice with decitabine on gestation Day 10 was associated with a reduced pregnancy rate resulting from effects on sperm production in the F1-generation.

8.2 Lactation

Risk Summary

There are no data on the presence of cedazuridine, decitabine, or their metabolites in human milk or on their effects on the breastfed child or milk production. Because of the potential for serious adverse reactions in the breastfed child, advise women not to breastfeed during treatment with INQOVI and for at least 2 weeks after the last dose.

8.3 Females and Males of Reproductive Potential

INQOVI can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*.

Pregnancy Testing

Verify the pregnancy status in females of reproductive potential prior to initiating INQOVI.

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment with INQOVI and for 6 months after the last dose.

Males

Based on genotoxicity findings, advise males with female partners of reproductive potential to use effective contraception during treatment with INQOVI and for 3 months after the last dose *[see Nonclinical Toxicology (13.1)]*.

Infertility

Based on findings of decitabine and cedazuridine in animals, INQOVI may impair male fertility *[see Nonclinical Toxicology (13.1)]*. The reversibility of the effect on fertility is unknown.

8.4 Pediatric Use

The safety and effectiveness of INQOVI have not been established in pediatric patients.

8.5 Geriatric Use

Of the 208 patients in clinical studies who received INQOVI, 75% were age 65 years and older, while 36% were age 75 years and older. No overall differences in safety or effectiveness were observed between patients age 65 years and older, 75 years and older, and younger patients.

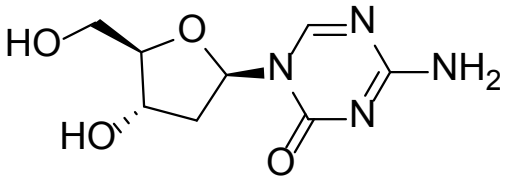
8.6 Renal Impairment

No dosage modification of INQOVI is recommended for patients with mild or moderate renal impairment (creatinine clearance [CLcr] of 30 to 89 mL/min based on Cockcroft-Gault). Due to the potential for increased adverse reactions, monitor patients with moderate renal impairment (CLcr 30 to 59 mL/min) frequently for adverse reactions. INQOVI has not been studied in patients with severe renal impairment (CLcr 15 to 29 mL/min) or end-stage renal disease (ESRD: CLcr <15 mL/min) *[see Clinical Pharmacology (12.3)]*.

11 DESCRIPTION

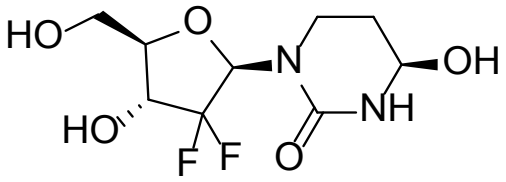
Decitabine

Decitabine is a nucleoside metabolic inhibitor. Decitabine is a white to off-white solid with the molecular formula of $C_8H_{12}N_4O_4$ and a molecular weight of 228.21 daltons. Its international union of pure and applied chemistry (IUPAC) chemical name is 4-amino-1-[(2*R*,4*S*,5*R*)-4-hydroxy-5-(hydroxymethyl)oxolan-2-yl]-1,3,5-triazin-2(1*H*)-one and it has the following structural formula:



Cedazuridine

Cedazuridine is a cytidine deaminase inhibitor. Cedazuridine is a white to off-white solid with the molecular formula of $C_9H_{14}F_2N_2O_5$ and a molecular weight of 268.21 daltons. Its IUPAC chemical name is (4*R*)-1-[(2*R*,4*R*,5*R*)-3,3-difluoro-4-hydroxy-5-(hydroxymethyl)oxolan-2-yl]-4-hydroxy-1,3-diazinan-2-one and it has the following structural formula:



INQOVI

INQOVI (decitabine and cedazuridine) tablets, for oral use contain 35 mg decitabine and 100 mg cedazuridine. The tablets are biconvex, oval-shaped, film-coated, red and debossed with "H35" on one side. Each film-coated tablet contains the following inactive ingredients: lactose monohydrate, hypromellose, croscarmellose sodium, colloidal silicon dioxide, and magnesium stearate. The film coating material contains polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, and iron oxide red.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Decitabine is a nucleoside metabolic inhibitor that is believed to exert its effects after phosphorylation and direct incorporation into DNA and inhibition of DNA methyltransferase, causing hypomethylation of DNA and cellular differentiation and/or apoptosis. Decitabine inhibits DNA methylation in vitro, which is achieved at concentrations that do not cause major suppression of DNA synthesis. Decitabine-induced hypomethylation in cancer cells may restore normal function to genes that are critical for the control of cellular differentiation and proliferation. In rapidly dividing cells, the cytotoxicity of decitabine may also be attributed to the formation of covalent adducts between DNA methyltransferase and decitabine incorporated into DNA. Non-proliferating cells are relatively insensitive to decitabine.

Cytidine deaminase (CDA) is an enzyme that catalyzes the degradation of cytidine, including the cytidine analog decitabine. High levels of CDA in the gastrointestinal tract and liver degrade decitabine and limit its oral bioavailability. Cedazuridine is a CDA inhibitor. Administration of cedazuridine with decitabine increases systemic exposure of decitabine.

12.2 Pharmacodynamics

Decitabine induced hypomethylation both in vitro and in vivo. In patients administered the recommended dosage of INQOVI, the maximum change from baseline in the long interspersed nucleotide elements-1 (LINE-1) demethylation was observed at Day 8, with less than complete recovery of LINE-1 methylation to baseline at the end of the treatment cycle.

Based on the exposure-response analyses, a relationship between an increase in 5-day cumulative daily decitabine exposure and a greater likelihood of some adverse reactions (e.g., any grade neutropenias, thrombocytopenia) was observed in clinical studies.

12.3 Pharmacokinetics

The pharmacokinetics of decitabine and cedazuridine following administration of INQOVI at the recommended dosage in patients with MDS and CMML are shown in Table 4.

The geometric mean ratio (GMR) of decitabine area under the curve (AUC) following the first dose of INQOVI compared to that of intravenous decitabine on Day 1 was 60% (90% confidence intervals (CI): 55, 65) in patients with MDS and CMML *[see Dosage and Administration (2.1)]*. The GMR of decitabine AUC following 5 consecutive once daily doses of INQOVI compared to that of intravenous decitabine on Day 5 was 106% (90% CI: 98, 114) and the GMR of the 5-day cumulative decitabine AUC following 5 consecutive once daily doses of INQOVI compared to that of intravenous decitabine was 99% (90% CI: 93, 106).

An approximately dose-proportional increase in peak concentrations (C_{max}) and AUC over the dosing interval was observed for decitabine following administration of oral decitabine at 20 mg to 40 mg once daily (0.6 to 1.1 times the recommended dose) in combination with 100 mg oral cedazuridine, and for cedazuridine following administration of oral cedazuridine at 40 to 100 mg once daily (0.4 to 1.0 times the recommended dose) in combination with 20 mg oral decitabine.

Table 4: Pharmacokinetics of the Components of INQOVI*

Parameter	Decitabine	Cedazuridine
General Information		
With the recommended dosage of INQOVI for 5 consecutive days:		
5-day cumulative AUC, ng.hr/mL	851 (50%)	--
Day 1 AUC, ng·hr/mL	103 (55%)	2950 (49%)
Steady state AUC, ng·hr/mL	178 (53%)	3291 (45%)
Time to steady state, days	2	2

Accumulation ratio based on AUC	1.7 (42%)	1.1 (63%)
C_{max}, ng/mL	145 (55%)	371 (52%)
Absorption		
Bioavailability	Cedazuridine increases oral decitabine exposure	20% (23%)
T_{max}, hours‡	1 (0.3 to 3.0)	3 (1.5 to 6.1)
Distribution		
V/F at steady state, L	417 (54%)	296 (51%)
Fraction unbound, in vitro	96% (4%) to 94% (2%) between 17 ng/mL to 342 ng/mL	66% (6%) to 62% (2%) between 1000 ng/mL and 50000 ng/mL
Elimination		
Half-life at steady state†, hours	1.5 (27%)	6.7 (19%)
CL/F at steady state, L/hours	197 (53%)	30.3 (46%)
Metabolism		
Primary Pathways	Primarily by cytidine deaminase (CDA) and by physicochemical degradation	Conversion to epimer by physicochemical degradation
Excretion§		
Total (% unchanged)	--	46% (21%) in urine and 51% (27%) in feces

C_{max}= maximum plasma concentration; AUC_{0-24h}=area under the plasma concentration-time curve from time zero to 24 hours; CV=coefficient of variation; SD=standard deviation; T_{max}= Time to maximum concentration; V/F=apparent volume of distribution; CL/F=apparent clearance

* Mean (%CV)

† Mean (SD)

‡ Median (range)

§ Healthy subjects

Specific Populations

Age (32 to 90 years), sex, and mild hepatic impairment (total bilirubin > 1 to 1.5 × ULN or AST > ULN) did not have an effect on the pharmacokinetics of decitabine or cedazuridine after dosing with INQOVI.

Decitabine exposure (AUC) increased with decreasing body surface area or body weight, and cedazuridine exposure increased with decreasing CLcr; however, body surface area (1.3 to 2.9 m^2), body weight (41 to 158 kg), and mild to moderate renal impairment (CLcr 30 to 89 mL/min based on Cockcroft Gault) did not have a clinically meaningful effect on the pharmacokinetics of decitabine and cedazuridine after dosing with INQOVI.

The effects of moderate (total bilirubin > 1.5 to 3 × ULN and any AST) and severe hepatic impairment (total bilirubin > 3 × ULN and any AST) or severe renal impairment (CLcr 15 to <30 mL/min) and ESRD (CLcr <15 mL/min) on the pharmacokinetics of decitabine and cedazuridine are unknown.

Drug Interaction Studies

Clinical Studies

Decitabine had no clinically meaningful effect on the pharmacokinetics of cedazuridine. Cedazuridine increased the exposure of decitabine.

The coadministration of INQOVI with proton pump inhibitors had no clinically meaningful effect on exposure to decitabine or cedazuridine.

In vitro Studies

CYP Enzymes: Cedazuridine is not a substrate of cytochrome P450 (CYP) enzymes. Cedazuridine does not induce CYP1A, CYP2B6, CYP2C9, or CYP3A or inhibit CYP1A, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A.

Transporter Systems: Cedazuridine is not a substrate of P-glycoprotein (P-gp), MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OAPT1B3, OATP2B1, OCT1, or OCT2, and does not inhibit P-gp, BCRP, MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, or OCT2.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies with decitabine, cedazuridine, or their combination have not been conducted.

INQOVI is genotoxic. Decitabine increased mutation frequency in L5178Y mouse lymphoma cells, and mutations were produced in an *E. coli* lac-I transgene in colonic DNA of decitabine-treated mice. Decitabine also caused chromosomal rearrangements in larvae of fruit flies. Cedazuridine was genotoxic in a reverse bacterial mutation assay (Ames assay) and in an in vitro chromosomal aberration study using human lymphocytes.

Fertility and repeat-dose toxicity studies in animals showed adverse outcomes on reproductive function and fertility. In male mice given intraperitoneal injections of 0.15, 0.3, or 0.45 mg/m^2 decitabine (approximately 0.3% to 1% the recommended clinical dose) 3 times a week for 7 weeks, testes weights were reduced, abnormal histology was observed, and significant decreases in sperm number were found at doses ≥ 0.3 mg/m^2. In females mated to males dosed with ≥ 0.3 mg/m^2 decitabine, pregnancy rate was reduced, and preimplantation loss was significantly increased.

Decitabine was administered orally to rats at 0.75, 2.5, or 7.5 mg/kg/day in cycles of 5-days-on/23-days-off for a total of 90 days. Low testes and epididymis weights, abnormal histology, and reduced sperm number were observed at doses ≥ 0.75 mg/kg. The dose of 0.75 mg/kg resulted in exposures in animals that were approximately 3 times the exposure in patients at the recommended clinical dose based on AUC.

Cedazuridine was administered orally to mice at 100, 300, or 1,000 mg/kg/day in cycles of 7-days-on/21-days-off for a total of 91 days. Adverse findings in male and female reproductive organs were observed at the 1,000 mg/kg dose and included abnormal histology in the testes and epididymis, reduced sperm number, and abnormal histology in the ovary. The dose of 1,000 mg/kg/day resulted in exposures in animals that were approximately 108 times the exposure in patients at the recommended clinical dose. Adverse effects in male and female reproductive organs were reversible following a recovery period.

14 CLINICAL STUDIES

Study ASTX727-01-B

INQOVI was evaluated in Study ASTX727-01-B, an open-label, randomized, 2-cycle, 2-sequence crossover study (NCT02103478) that included 80 adult patients with MDS (International Prognostic Scoring System [IPSS] Intermediate-1, Intermediate-2, or high-risk) or CMML. Patients were randomized 1:1 to receive INQOVI (35 mg decitabine and 100 mg cedazuridine) orally in Cycle 1 and decitabine 20 mg/m^2 intravenously in Cycle 2 or the reverse sequence. Both INQOVI and intravenous decitabine were administered once daily on Days 1 through 5 of the 28-day cycle. Starting with Cycle 3, all patients received INQOVI orally once daily on Days 1 through 5 of each 28-day cycle until disease progression or unacceptable toxicity. Randomization was stratified by IPSS risk level. Twelve (15%) of the 80 patients went on to stem cell transplantation following INQOVI treatment.

The baseline demographic and disease characteristics are shown in Table 5.

Table 5: Demographics and Baseline Disease Characteristics for Study ASTX727-01-B

Characteristic	**N=80**
Age	
Median (min, max) (years)	71 (32, 90)
Sex (%)	
Male	76
Female	24
Race (%)	
White	93
Black or African American	3

Characteristic	N=80
Asian	1
Other or Not Reported	4
ECOG Performance Score (%)	
0	44
1	48
2	9
Disease Category / IPSS (%)	
MDS INT-1	44
MDS INT-2	24
MDS High-Risk	11
CMML	21
Prior HMA Therapy[*] (%)	
Prior Azacitidine	4
Prior Decitabine	4
Transfusion Dependence[†] (%)	
RBC Transfusion Dependence	48
Platelet Transfusion Dependence	15

[*] One cycle only, per the Exclusion Criteria.

[†] Defined as documentation of ≥ 2 units of transfusion within 56 days prior to the first day of study treatment.

Efficacy was established on the basis of complete response (CR) and the rate of conversion from transfusion dependence to transfusion independence. Efficacy results are shown in Table 6. The median follow-up time was 24.0 months (range: 12.0 to 28.8 months) and median treatment duration was 6.6 months (range < 0.1 to 27.9).

Table 6: Efficacy Results in Patients with MDS or CMML from Study ASTX727-01-B

Efficacy Endpoint	INQOVI N=80
Complete Response (%) (95% CI)	18 (10, 28)
Median Duration of CR - months (range)*	8.7 (1.1, 18.2)
Median Time to CR - months (range)	4.8 (1.7, 10.0)

* From start of CR until relapse or death.

Among the 41 patients who were dependent on red blood cell (RBC) and/or platelet transfusions at baseline, 20 (49%) became independent of RBC and platelet transfusions during any consecutive 56-day post-baseline period. Of the 39 patients who were independent of both RBC and platelet transfusions at baseline, 25 (64%) remained transfusion-independent during any consecutive 56-day post-baseline period.

Study ASTX727-02

INQOVI was evaluated in ASTX727-02, an open-label, randomized, 2-cycle, 2-sequence crossover study (NCT03306264) that included 133 adult patients with MDS or CMML, including all French-American-British (FAB) classification criteria and IPSS Intermediate-1, Intermediate-2, or high-risk prognostic scores. Patients were randomized 1:1 to receive INQOVI (35 mg decitabine and 100 mg cedazuridine) orally in Cycle 1 and decitabine 20 mg/m^2 intravenously in Cycle 2 or the reverse sequence. Both INQOVI and intravenous decitabine were administered once daily on Days 1 through 5 of the 28-day cycle. Starting with Cycle 3, all patients received INQOVI orally once daily on Days 1 through 5 of each 28-day cycle until disease progression or unacceptable toxicity. No stratification was performed. Twenty-seven (20%) of the 133 patients went on to stem cell transplantation following INQOVI treatment.

The baseline demographic and disease characteristics are shown in Table 7.

Table 7: Demographics and Baseline Disease Characteristics for Study ASTX727-02

Characteristic	N=133
Age (years)	
Median (min, max)	71 (44, 88)
Sex (%)	
Male	65
Female	35
Race (%)	
White	91

Black or African American	3
Asian	2
Other or Not Reported	4
ECOG Performance Score (%)	
0	41
1	59
Disease Category / IPSS (%)	
MDS INT-1	44
MDS INT-2	20
MDS High Risk	16
MDS Low Risk	8
CMML	12
Prior HMA Therapy[*] (%)	
Prior Azacitidine	5
Prior Decitabine	3
Transfusion Dependence[†] (%)	
RBC Transfusion Dependence	39
Platelet Transfusion Dependence	8

[*] One cycle only, per the Exclusion Criteria.

[†] Defined as documentation of ≥ 2 units of transfusion within 56 days prior to the first day of study treatment.

The primary outcome measure was comparison of the 5-day cumulative decitabine AUC between INQOVI and intravenous decitabine *[see Clinical Pharmacology (12.3)]*. Efficacy was established on the basis of complete response (CR) and the rate of conversion from transfusion dependence to transfusion independence. Efficacy results are shown in Table 8. The median follow-up time was 12.6 months (range: 9.3 to 20.5) and median treatment duration was 8.2 months (range 0.2 to 19.7).

Table 8: Efficacy Results in Patients with MDS or CMML from Study ASTX727-02

Efficacy Endpoints	INQOVI (N=133)
Complete Response (%) (95% CI)	21 (15, 29)
Median Duration of CR - months (range)*	7.5 (1.6, 17.5)
Median Time to CR - months (range)	4.3 (2.1, 15.2)

* From start of CR until relapse or death.

Among the 57 patients who were dependent on RBC and/or platelet transfusions at baseline, 30 (53%) became independent of RBC and platelet transfusions during any 56-day post-baseline period. Of the 76 patients who were independent of both RBC and platelet transfusions at baseline, 48 (63%) remained transfusion-independent during any 56-day post-baseline period.

15 REFERENCES

1. OSHA Hazardous Drugs. *OSHA*. http://www.osha.gov/SLTC/hazardousdrugs/index.html

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

INQOVI tablets are biconvex, oval-shaped, film-coated, red, and debossed with "H35" on one side.

The tablets are packaged in blisters and supplied as follows:

- NDC: 64842-0727-9; 5 tablets in one blister card in a child-resistant carton

Storage and Handling

Store at 20°C to 25°C (68°F to 77°F); excursions permitted from 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Dispense medication in the original packaging.

INQOVI is a hazardous drug. Follow applicable special handling and disposal procedures.[1]

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Myelosuppression

Advise patients of the risk of myelosuppression and to report any symptoms of fever, infection, anemia, or bleeding to their healthcare provider as soon as possible. Advise patients for the need for laboratory monitoring *[see Warnings and Precautions (5.1)]*.

Embryo-Fetal Toxicity

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.2), Use in Specific Populations (8.1)]*.

Advise females of reproductive potential to use effective contraception during treatment with INQOVI and for 6 months after the last dose *[see Use in Specific Populations (8.3)]*.

Advise males with female partners of reproductive potential to use effective contraception during treatment with INQOVI and for 3 months after the last dose *[see Use in Specific Populations (8.3), Nonclinical Toxicology (13.1)]*.

Lactation

Advise women not to breastfeed during treatment with INQOVI and for 2 weeks after the last dose *[see Use in Specific Populations (8.2)]*.

Administration

Advise patients to take INQOVI at approximately the same time each day on an empty stomach. Instruct patients to avoid eating for at least 2 hours before and 2 hours after taking INQOVI. Advise patients on what to do when a dose is missed or vomited *[see Dosage and Administration (2.2)]*.

Manufactured for:
Otsuka Pharmaceutical Co., Ltd.
Japan

Distributed by:
Taiho Oncology, Inc.
Princeton, NJ 08540 USA

LONSURF® (FTD/TPI) tablets dosing guide

Starting dose based on trial results in mCRC and metastatic gastric or GEJ cancer[1-5]*

Dosing guidelines[1]

Indicated dosage	35 mg/m² twice daily[ab]
Active treatment days	Days 1 to 5 and 8 to 12 of each 28-day treatment cycle
BSA-based calculation	• Round up to the nearest 5 mg increment • Do not exceed 80 mg/dose[a] or 160 mg/day[a]
Administration	• Taken orally twice daily with food • No restriction on food type
Missed or vomited doses	The patient should not make up for these doses
Handling	LONSURF is a cytotoxic drug. Follow applicable special handling and disposal procedures

[a]Based on the trifluridine component.
[b]In patients with severe renal impairment (CLcr of 15 to 29 mL/min), the recommended dosage is 20 mg/m².

28-day dosing schedule[1]

Week 1	Twice daily for 5 days with food	2 days rest
Week 2	Twice daily for 5 days with food	2 days rest
Week 3	Rest	
Week 4	Rest	

- Obtain complete blood cell counts prior to and on day 15 of each cycle

2 tablet strengths for personalized dosing[1]

15 mg trifluridine/
6.14 mg tipiracil tablet

20 mg trifluridine/
8.19 mg tipiracil tablet

Tablets shown at actual size.

BSA=body surface area; CLcr=creatinine clearance; FTD/TPI=trifluridine/tipiracil; GEJ=gastroesophageal junction; mCRC=metastatic colorectal cancer; OS=overall survival; PFS=progression-free survival; RECOURSE=Refractory Colorectal Cancer Study (Study 1); TAGS=TAS-102 Gastric Study.

*In the RECOURSE study: median OS (95% CI): 7.2 months (6.6-7.8) for LONSURF vs 5.2 months (4.6-5.9) for placebo (HR=0.69 [95% CI: 0.59-0.81]; $P<0.0001$). Number (%) of deaths was 364 (68) for LONSURF and 210 (79) for placebo. RECOURSE was a randomized, double-blind, placebo-controlled phase 3 study. Treatment arms were LONSURF plus best supportive care (BSC) vs placebo plus BSC. All patients were 18 years of age, had Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and had received at least 2 prior regimens of standard chemotherapy and were refractory to or were failing all of the following within 3 months: fluoropyrimidine, irinotecan, and oxaliplatin; an anti-VEGF biological therapy; and an anti-EGFR therapy (if *RAS* wild type). The primary efficacy endpoint was OS. Key secondary endpoints included PFS and safety and tolerability.[1-4]

In the TAGS study, median OS (95% CI): 5.7 months (4.8-6.2) for LONSURF vs 3.6 months (3.1-4.1) for placebo (HR=6.9 [95% CI: 0.56-0.85]; $P=0.0006$). TAGS was a multinational, randomized, double-blind, placebo-controlled, phase 3 trial. Treatment arms were LONSURF plus BSC vs placebo plus BSC. All patients were 18 years of age (≥20 years of age in Japan), had histologically confirmed, nonresectable, metastatic gastric or GEJ adenocarcinoma, had ECOG performance status of 0 or 1, had previously received 2 regimens of standard chemotherapy, and were refractory to or intolerant of their last previous therapy. Previous regimens must have included a fluoropyrimidine, a platinum agent, a taxane or irinotecan, or both, and, if HER2-positive, an anti-HER2 therapy. Adjuvant chemotherapy could be counted as 1 prior regimen in patients who had recurrence during or within 6 months of completion of the adjuvant chemotherapy. Both patients and investigators were masked to treatment allocation. The primary endpoint was OS. Key secondary endpoints included PFS and safety and tolerability.[1,3,5]

For assistance in calculating your patient's LONSURF starting dose, use the dosage calculator online at LONSURFhcp.com/calculator

Please see Important Safety Information on page 2 and full Prescribing Information starting on page 3.

Lonsurf®
(trifluridine and tipiracil) tablets

LONSURF is indicated for the treatment of adult patients with metastatic colorectal cancer previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and if *RAS* wild-type, an anti-EGFR therapy.

LONSURF is indicated for the treatment of adult patients with metastatic gastric or gastroesophageal junction adenocarcinoma previously treated with at least two prior lines of chemotherapy that included a fluoropyrimidine, a platinum, either a taxane or irinotecan, and if appropriate, HER2/neu-targeted therapy.

Important Safety Information

WARNINGS AND PRECAUTIONS

Severe Myelosuppression:

LONSURF caused severe and life-threatening myelosuppression (Grade 3-4) consisting of neutropenia (38%), anemia (18%), thrombocytopenia (5%), and febrile neutropenia (3%). Two patients (0.2%) died due to neutropenic infection. A total of 12% of LONSURF-treated patients received granulocyte-colony stimulating factors. Obtain complete blood counts prior to and on day 15 of each cycle of LONSURF and more frequently as clinically indicated. Withhold LONSURF for febrile neutropenia, absolute neutrophil count less than 500/mm^3, or platelets less than 50,000/mm^3. Upon recovery, resume LONSURF at a reduced dose as clinically indicated.

Embryo-Fetal Toxicity:

LONSURF can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to the fetus. Advise females of reproductive potential to use effective contraception during treatment and for at least 6 months after the final dose.

USE IN SPECIFIC POPULATIONS

Lactation: It is not known whether LONSURF or its metabolites are present in human milk. There are no data to assess the effects of LONSURF or its metabolites on the breast-fed infant or the effects on milk production. Because of the potential for serious adverse reactions in breast-fed infants, advise women not to breastfeed during treatment with LONSURF and for 1 day following the final dose.

Male Contraception: Because of the potential for genotoxicity, advise males with female partners of reproductive potential to use condoms during treatment with LONSURF and for at least 3 months after the final dose.

Geriatric Use: Patients 65 years of age or over who received LONSURF had a higher incidence of the following compared to patients younger than 65 years: Grade 3 or 4 neutropenia (46% vs 32%), Grade 3 anemia (22% vs 16%), and Grade 3 or 4 thrombocytopenia (7% vs 4%).

Hepatic Impairment: Do not initiate LONSURF in patients with baseline moderate or severe (total bilirubin greater than 1.5 times ULN and any AST) hepatic impairment. Patients with severe hepatic impairment (total bilirubin greater than 3 times ULN and any AST) were not studied. No adjustment to the starting dose of LONSURF is recommended for patients with mild hepatic impairment.

Renal Impairment: No adjustment to the starting dosage of LONSURF is recommended in patients with mild or moderate renal impairment (CLcr of 30 to 89 mL/min). Reduce the starting dose of LONSURF for patients with severe renal impairment (CLcr of 15 to 29 mL/min) to a recommended dosage of 20 mg/m^2.

ADVERSE REACTIONS

Most Common Adverse Drug Reactions in Patients Treated With LONSURF (≥5%): The most common adverse drug reactions in LONSURF-treated patients vs placebo-treated patients with mCRC, respectively, were asthenia/fatigue (52% vs 35%), nausea (48% vs 24%), decreased appetite (39% vs 29%), diarrhea (32% vs 12%), vomiting (28% vs 14%), infections (27% vs 16%), abdominal pain (21% vs 18%), pyrexia (19% vs 14%), stomatitis (8% vs 6%), dysgeusia (7% vs 2%), and alopecia (7% vs 1%). In metastatic gastric cancer or gastroesophageal junction (GEJ), the most common adverse drug reactions, respectively were, nausea (37% vs 32%), decreased appetite (34% vs 31%), vomiting (25% vs 20%), infections (23% vs 16%) and diarrhea (23% vs 14%).

Pulmonary emboli occurred more frequently in LONSURF-treated patients compared to placebo: in mCRC (2% vs 0%) and in metastatic gastric cancer and GEJ (3% vs 2%).

Interstitial lung disease (0.2%), including fatalities, has been reported in clinical studies and clinical practice settings in Asia.

Laboratory Test Abnormalities in Patients Treated With LONSURF: The most common laboratory test abnormalities in LONSURF-treated patients vs placebo-treated patients with mCRC, respectively, were anemia (77% vs 33%), neutropenia (67% vs 1%), and thrombocytopenia (42% vs 8%). In metastatic gastric cancer or GEJ, the test abnormalities, respectively, were neutropenia (66% vs 4%), anemia (63% vs 38%), and thrombocytopenia (34% vs 9%).

Please see full Prescribing Information starting on page 3.

References: 1. LONSURF [package insert]. Princeton, NJ: Taiho Oncology, Inc.; 2019. **2.** Van Cutsem E, Mayer RJ, Laurent S, et al; for the RECOURSE Study Group. The subgroups of the phase III RECOURSE trial of trifluridine/tipiracil (TAS-102) versus placebo with best supportive care in patients with metastatic colorectal cancer. *Eur J Cancer.* 2018;90:63-72. **3.** Data on file. Taiho Oncology, Inc., Princeton, NJ. **4.** Mayer RJ, Van Cutsem E, Falcone A, et al; for the RECOURSE Study Group. Randomized trial of TAS-102 for refractory metastatic colorectal cancer. *N Engl J Med.* 2015;372(20):1909-1919. **5.** Shitara K, Doi T, Dvorkin M, et al. Trifluridine/tipiracil versus placebo in patients with heavily pretreated metastatic gastric cancer (TAGS): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol.* 2018;19(11):1437-1448.

TAIHO ONCOLOGY

Lonsurf®
(trifluridine and tipiracil) tablets

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use LONSURF safely and effectively. See full prescribing information for LONSURF.

LONSURF (trifluridine and tipiracil) tablets, for oral use
Initial U.S. Approval: 2015

RECENT MAJOR CHANGES

Indications and Usage (1.2)	2/2019
Recommended Dosage (2.1)	2/2019
Warnings and Precaution (5.1)	2/2019

INDICATIONS AND USAGE

LONSURF is a combination of trifluridine, a nucleoside metabolic inhibitor, and tipiracil, a thymidine phosphorylase inhibitor, indicated for the treatment of adult patients with:

- metastatic colorectal cancer who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and if RAS wild-type, an anti-EGFR therapy. (1.1)
- metastatic gastric or gastroesophageal junction adenocarcinoma previously treated with at least two prior lines of chemotherapy that included a fluoropyrimidine, a platinum, either a taxane or irinotecan, and if appropriate, HER2/neu-targeted therapy. (1.2)

DOSAGE AND ADMINISTRATION

- Recommended Dosage: 35 mg/m^2/dose orally twice daily with food on Days 1 through 5 and Days 8 through 12 of each 28-day cycle. (2.1)

DOSAGE FORMS AND STRENGTHS

Tablets:

- 15 mg trifluridine/6.14 mg tipiracil (3)
- 20 mg trifluridine/8.19 mg tipiracil (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Severe Myelosuppression: Obtain complete blood counts prior to and on Day 15 of each cycle. Withhold and resume at next lower LONSURF dosage as recommended. (2.1, 5.1)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception. (5.2, 8.1, 8.3)

ADVERSE REACTIONS

The most common adverse reactions or laboratory abnormalities (≥10%) are anemia, neutropenia, fatigue/asthenia, nausea, thrombocytopenia, decreased appetite, diarrhea, vomiting, and pyrexia (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Taiho Oncology, Inc. at 1-844-878-2446 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

- Lactation: Advise not to breastfeed. (8.2)
- Geriatric Use: Grade 3 or 4 neutropenia and thrombocytopenia and Grade 3 anemia occurred more commonly in patients 65 years or older. (8.5)
- Hepatic Impairment: Do not initiate LONSURF in patients with baseline moderate or severe hepatic impairment. (8.7)
- Renal Impairment: Reduce LONSURF dose in patients with severe renal impairment. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 12 /2019

FULL PRESCRIBING INFORMATION: CONTENTS*

***Sections or subsections omitted from the full prescribing information are not listed.**

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Metastatic Colorectal Cancer

LONSURF is indicated for the treatment of adult patients with metastatic colorectal cancer previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and if RAS wild-type, an anti-EGFR therapy.

1.2 Metastatic Gastric Cancer

LONSURF is indicated for the treatment of adult patients with metastatic gastric or gastroesophageal junction adenocarcinoma previously treated with at least two prior lines of chemotherapy that included a fluoropyrimidine, a platinum, either a taxane or irinotecan, and if appropriate, HER2/neu-targeted therapy.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dosage of LONSURF is 35 mg/m^2 up to a maximum of 80 mg per dose (based on the trifluridine component) orally twice daily with food on Days 1 through 5 and Days 8 through 12 of each 28-day cycle until disease progression or unacceptable toxicity. Round dose to the nearest 5 mg increment.

Instruct patients to swallow LONSURF tablets whole.

Instruct patients not to retake doses of LONSURF that are vomited or missed and to continue with the next scheduled dose.

LONSURF is a cytotoxic drug. Follow applicable special handling and disposal procedures.[1]

Table 1 shows the calculated initial daily dose based on body surface area (BSA).

Table 1 Recommended Dosage According to Body Surface Area (BSA)

BSA (m2)	Total daily dose (mg)	Dose (mg) administered twice daily	Tablets per dose	
			15mg	20mg
< 1.07	70	35	1	1
1.07 - 1.22	80	40	0	2
1.23 - 1.37	90	45	3	0
1.38 - 1.52	100	50	2	1
1.53 - 1.68	110	55	1	2
1.69 - 1.83	120	60	0	3
1.84 - 1.98	130	65	3	1
1.99 - 2.14	140	70	2	2
2.15 - 2.29	150	75	1	3
≥2.30	160	80	0	4

2.2 Dosage Modifications for Adverse Reactions

Obtain complete blood cell counts prior to and on Day 15 of each cycle *[see Warnings and Precautions (5.1)]*.

Do not initiate the cycle of LONSURF until:

- Absolute neutrophil count (ANC) greater than or equal to 1,500/mm^3 or febrile neutropenia is resolved
- Platelets greater than or equal to 75,000/mm^3
- Grade 3 or 4 non-hematological adverse reactions are resolved to Grade 0 or 1

Within a treatment cycle, withhold LONSURF for any of the following:

- Absolute neutrophil count (ANC) less than 500/mm^3 or febrile neutropenia
- Platelets less than 50,000/mm^3
- Grade 3 or 4 non-hematologic adverse reaction

After recovery, resume LONSURF after reducing the dose by 5 mg/m^2/dose from the previous dose, if the following occur:

- Febrile neutropenia
- Uncomplicated Grade 4 neutropenia (which has recovered to greater than or equal to 1,500/mm^3) or thrombocytopenia (which has recovered to greater than or equal to 75,000/mm^3) that results in more than 1 week delay in start of next cycle
- Non-hematologic Grade 3 or Grade 4 adverse reaction except for Grade 3 nausea and/or vomiting controlled by antiemetic therapy or Grade 3 diarrhea responsive to antidiarrheal medication

A maximum of 3 dose reductions are permitted. Permanently discontinue LONSURF in patients who are unable to tolerate a dose of 20 mg/m^2 orally twice daily. Do not escalate LONSURF dosage after it has been reduced.

2.3 Recommended Dosage for Renal Impairment

Severe Renal Impairment

In patients with severe renal impairment [creatinine clearance (CLcr) of 15 to 29 mL/min as determined by the Cockcroft-Gault formula], the recommended dosage is 20 mg/m^2 (based on the trifluridine component) orally twice daily with food on Days 1 through 5 and Days 8 through 12 of each 28-day cycle (Table 2) *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*. Reduce dose to 15 mg/m^2 twice daily in patients with severe renal impairment who are unable to tolerate a dose of 20 mg/m^2 twice daily (Table 2). Permanently discontinue LONSURF in patients who are unable to tolerate a dose of 15 mg/m^2 twice daily.

Table 2 Recommended Dosage for Severe Renal Impairment According to BSA

BSA (m^2)	Total daily dose (mg)	Dose (mg) administered twice daily	Tablets per dose	
			15mg	20mg
For a dose of 20 mg/m^2 twice daily:				
< 1.14	40	20	0	1
1.14 – 1.34	50	25*	2 in the evening*	1 in the morning*
1.35 – 1.59	60	30	2	0
1.60 – 1.94	70	35	1	1
1.95 – 2.09	80	40	0	2
2.10 – 2.34	90	45	3	0
≥ 2.35	100	50	2	1
For a dose of 15 mg/m^2 twice daily:				
< 1.15	30	15	1	0
1.15 – 1.49	40	20	0	1
1.50 – 1.84	50	25*	2 in the evening*	1 in the morning*
1.85 – 2.09	60	30	2	0
2.10 – 2.34	70	35	1	1
≥ 2.35	80	40	0	2

* For a total daily dose of 50 mg, instruct patients to take 1 x 20-mg tablet in the morning and 2 x 15-mg tablets in the evening.

3 DOSAGE FORMS AND STRENGTHS

Tablets:

- 15 mg trifluridine/6.14 mg tipiracil: white, biconvex, round, film-coated, imprinted with ‘15’ on one side, and ‘102’ and ‘15 mg’ on the other side, in gray ink.
- 20 mg trifluridine/8.19 mg tipiracil: pale red, biconvex, round, film-coated, imprinted with ‘20’ on one side, and ‘102’ and ‘20 mg’ on the other side, in gray ink.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Severe Myelosuppression

In the 868 patients who received LONSURF in RECOURSE and TAGS, LONSURF caused severe and life-threatening myelosuppression (Grade 3-4) consisting of anemia (18%), neutropenia (38%), thrombocytopenia (5%) and febrile neutropenia (3%). Two patients (0.2%) died due to neutropenic infection/sepsis and four other patients (0.5%) died due to septic shock. A total of 12% of LONSURF-treated patients received granulocyte-colony stimulating factors.

Obtain complete blood counts prior to and on Day 15 of each cycle of LONSURF and more frequently as clinically indicated. Withhold LONSURF for severe myelosuppression and resume at the next lower dosage *[*see *Dosage and Administration (2.2)]*.

5.2 Embryo-Fetal Toxicity

Based on animal studies and its mechanism of action, LONSURF can cause fetal harm when administered to a pregnant woman. Trifluridine/tipiracil caused embryo-fetal lethality and embryo-fetal toxicity in pregnant rats when orally administered during gestation at dosage levels resulting in exposures lower than those achieved at the recommended dosage of 35 mg/m^2 twice daily. Advise pregnant women of the potential risk to the fetus. Advise females of reproductive potential to use an effective method of contraception during treatment with LONSURF and for at least 6 months after the final dose *[*see *Use in Specific Populations (8.1, 8.3)]*.

6 ADVERSE REACTIONS

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

- Severe Myelosuppression *[*see *Warnings and Precautions (5.1)]*

6.1 Clinical Trials Experience

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

The data in the WARNINGS AND PRECAUTIONS section and below reflect exposure to LONSURF at the recommended dose in 533 patients with metastatic colorectal cancer in RECOURSE and 335 patients with metastatic gastric cancer in TAGS. Among the 868 patients who received LONSURF, 11% were exposed for 6 months or longer and 1% were exposed for 12 months or longer. The most common adverse reactions or laboratory abnormalities (≥10%) are anemia, neutropenia, fatigue/asthenia, nausea, thrombocytopenia, decreased appetite, diarrhea, vomiting, and pyrexia.

Metastatic Colorectal Cancer

The safety of LONSURF was evaluated in RECOURSE, a randomized (2:1), double-blind, placebo-controlled trial in patients with previously treated metastatic colorectal cancer *[see Clinical Studies (14.1)]*. Patients received LONSURF 35 mg/m^2/dose (n=533) or placebo (n=265) twice daily on Days 1 through 5 and Days 8 through 12 of each 28-day cycle. In RECOURSE, 12% of patients received LONSURF for more than 6 months and 1% of patients received LONSURF for more than 1 year.

The study population characteristics were: median age 63 years; 61% male; 57% White, 35% Asian, and 1% Black.

The most common adverse reactions or laboratory abnormalities (≥10% in incidence) in patients treated with LONSURF at a rate that exceeds the rate in patients receiving placebo were anemia, neutropenia, asthenia/fatigue, nausea, thrombocytopenia, decreased appetite, diarrhea, vomiting, abdominal pain, and pyrexia.

In RECOURSE, 3.6% of patients discontinued LONSURF for an adverse reaction and 14% of patients required a dose reduction. The most common adverse reactions or laboratory abnormalities leading to dose reduction were neutropenia, anemia, febrile neutropenia, fatigue, and diarrhea.

Tables 3 and 4 list the adverse reactions and laboratory abnormalities (graded using CTCAE v4.03), respectively, observed in RECOURSE.

Table 3 Adverse Reactions (≥5%) in Patients Receiving LONSURF and at a Higher Incidence (>2%) than in Patients Receiving Placebo in RECOURSE

Adverse Reactions	LONSURF (N=533)		Placebo (N=265)	
	All Grades (%)	Grades 3-4* (%)	All Grades (%)	Grades 3-4* (%)
General				
Asthenia/fatigue	52	7	35	9
Pyrexia	19	1	14	<1
Gastrointestinal				
Nausea	48	2	24	1
Diarrhea	32	3	12	<1
Vomiting	28	2	14	<1
Abdominal pain	21	2	18	4
Stomatitis	8	<1	6	0
Metabolism and nutrition				
Decreased appetite	39	4	29	5
Infections†	27	6	16	5
Nervous system				
Dysgeusia	7	0	2	0
Skin and subcutaneous tissue				
Alopecia	7	0	1	0

*No Grade 4 definition for nausea, abdominal pain, or fatigue in National Cancer Institute Common Terminology
†Incidence reflects 64 preferred terms in the Infections and Infestations system organ class.

Table 4 Laboratory Abnormalities in RECOURSE

Laboratory Parameter*	LONSURF		Placebo	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Hematologic				
Anemia†	77	18	33	3
Neutropenia	67	38	1	0
Thrombocytopenia	42	5	8	<1

* Worst Grade at least one grade higher than baseline, with percentages based on number of patients with post-baseline samples, which may be <533 (LONSURF) or 265 (placebo)
† One Grade 4 anemia adverse reaction based on clinical criteria was reported

In RECOURSE, pulmonary emboli occurred more frequently in LONSURF-treated patients (2%) compared to no patients on placebo.

Metastatic Gastric Cancer

The safety of LONSURF was evaluated in TAGS, an international, randomized (2:1), double-blind, placebo-controlled trial in patients with metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma who were previously treated with at least 2 prior chemotherapy regimens for advanced disease *[see Clinical Studies (14.2)]*. Previous treatments must have included a fluoropyrimidine, a platinum, and either a taxane or irinotecan. Patients with HER2/neu-positive tumors must have received prior HER2/neu-targeted therapy, if available. Adjuvant chemotherapy could be counted as one prior regimen in patients who had recurrence during or within 6 months of completion of the adjuvant chemotherapy. Patients received LONSURF 35 mg/m^2/dose (n=335) or placebo (n=168) twice daily on Days 1 through 5 and Days 8 through 12 of each 28-day cycle with best supportive care. In TAGS, 10% of patients received LONSURF for more than 6 months and 0.9% of patients received LONSURF for more than 1 year.

The study population characteristics were: median age 63 years (24 to 89 years); 73% male; 70% White, 16% Asian, and 1% Black.

The most common adverse reactions or laboratory abnormalities (≥10% in incidence) in patients treated with LONSURF at a rate that exceeds the rate in patients receiving placebo were neutropenia, anemia, nausea, decreased appetite, thrombocytopenia, vomiting, and diarrhea.

In TAGS, 13% of patients discontinued LONSURF for an adverse reaction and 11% of patients required a dose reduction. The most common adverse reactions or laboratory abnormalities leading to dose reduction were neutropenia, anemia, febrile neutropenia, and diarrhea.

Tables 5 and 6 list the adverse reactions and laboratory abnormalities (graded using CTCAE v4.03), respectively, observed in TAGS.

Table 5 Adverse Reactions (≥5%) in Patients Receiving LONSURF and at a Higher Incidence (>2%) than in Patients Receiving Placebo in TAGS

Adverse Reactions	LONSURF (N=335)		Placebo (N=168)	
	All Grades (%)	Grades 3-4* (%)	All Grades (%)	Grades 3-4* (%)
Gastrointestinal				
Nausea	37	3	32	3
Vomiting	25	4	20	2
Diarrhea	23	3	14	2
Metabolism and nutrition				
Decreased appetite	34	9	31	7
Infections†	23	5	16	5

*No Grade 4 definition for nausea or fatigue in NCI CTCAE, version 4.03.
†Incidence reflects 46 preferred terms in the Infections and Infestations system organ class.

Table 6 Laboratory Abnormalities in TAGS

Laboratory Parameter*	LONSURF		Placebo	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Hematologic				
Neutropenia	66	38	4	0
Anemia†	63	19	38	7
Thrombocytopenia	34	6	9	0

* Worst Grade at least one Grade higher than baseline, with percent based on number of patients with post-baseline samples which may be <335 (LONSURF) or 168 (placebo)
† Anemia: No Grade 4 definition in CTCAE, v4.03

In TAGS, pulmonary emboli occurred more frequently in LONSURF-treated patients (3.1%) compared to 1.8% for patients on placebo.

Additional Clinical Experience

Interstitial lung disease was reported in 15 (0.2%) patients, 3 of which were fatal, among approximately 7,000 patients exposed to LONSURF in clinical studies and clinical practice settings in Asia.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on animal data and its mechanism of action *[see Clinical Pharmacology (12.2)]*, LONSURF can cause fetal harm. LONSURF caused embryo-fetal lethality and embryo-fetal toxicity in pregnant rats when given during gestation at doses resulting in exposures lower than or similar to human exposures at the recommended clinical dose *(see Data).* There are no available data on LONSURF use in pregnant women. Advise pregnant women of the potential risk to a fetus.

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

Data

Animal Data

Trifluridine/tipiracil was administered orally once daily to female rats during organogenesis at dose levels of 15, 50, and 150 mg/kg [trifluridine (FTD) equivalent]. Decreased fetal weight was observed at FTD doses ≥50 mg/kg (approximately 0.33 times the FTD exposure at the clinical dose of 35 mg/m^2 twice daily). At the FTD dose of 150 mg/kg (approximately 0.92 times the FTD exposure at the clinical dose of 35 mg/m^2 twice daily) embryolethality and structural anomalies (kinked tail, cleft palate, ectrodactyly, anasarca, alterations in great vessels, and skeletal anomalies) were observed.

8.2 Lactation

Risk Summary

There are no data on the presence of trifluridine, tipiracil or its metabolites in human milk or its effects on the breastfed child or on milk production. In nursing rats, trifluridine and tipiracil or their metabolites were present in breast milk *(see Data)*. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with LONSURF and for 1 day following the final dose.

Data

Radioactivity was excreted in the milk of nursing rats dosed with trifluridine/tipiracil containing ^{14}C-FTD or ^{14}C-tipiracil (TPI). Levels of FTD-derived radioactivity were as high as approximately 50% of the exposure in maternal plasma an hour after dosing with trifluridine/tipiracil and were approximately the same as those in maternal plasma for up to 12 hours following dosing. Exposure to TPI-derived radioactivity was higher in milk than in

maternal plasma beginning 2 hours after dosing and continuing for at least 12 hours following administration of trifluridine/tipiracil.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating LONSURF *[see Use in Specific Populations (8.1)]*.

Contraception

LONSURF can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*.

Females

Advise females of reproductive potential to use effective contraception during treatment with LONSURF and for at least 6 months after the final dose.

Males

Because of the potential for genotoxicity, advise males with female partners of reproductive potential to use condoms during treatment with LONSURF and for at least 3 months after the final dose *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

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

Juvenile Animal Toxicity Data

Dental toxicity including whitening, breakage, and malocclusion (degeneration and disarrangement in the ameloblasts, papillary layer cells and odontoblasts) were observed in rats treated with trifluridine/tipiracil at doses ≥ 50 mg/kg (approximately 0.33 times the exposure at the clinical dose of 35 mg/m^2 twice daily).

8.5 Geriatric Use

In RECOURSE and TAGS, 868 patients received LONSURF; 45% were 65 years of age or over, while 10% were 75 and over. No overall differences in effectiveness were observed in patients 65 or older versus younger patients. Patients 65 years of age or older who received LONSURF had a higher incidence of the following hematologic laboratory abnormalities compared to patients younger than 65 years: Grade 3 or 4 neutropenia (46% vs. 32%), Grade 3 anemia (22% vs. 16%), and Grade 3 or 4 thrombocytopenia (7% vs. 4%).

8.6 Renal Impairment

No dose adjustment is recommended for patients with mild or moderate renal impairment (CLcr of 30 to 89 mL/min as determined by the Cockcroft-Gault formula). Reduce the dose of LONSURF for patients with severe renal impairment (CLcr of 15 to 29 mL/min) *[see Dosage and Administration (2.3)]*. The pharmacokinetics of trifluridine and tipiracil have not been studied in patients with end stage renal disease.

8.7 Hepatic Impairment

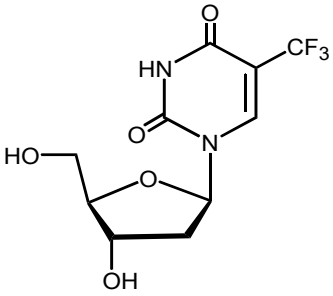
No adjustment to the starting dosage of LONSURF is recommended for patients with mild hepatic impairment. Do not initiate LONSURF in patients with baseline moderate or severe (total bilirubin >1.5 times ULN and any AST) hepatic impairment *[see Clinical Pharmacology (12.3)]*.

11 DESCRIPTION

LONSURF contains trifluridine and tipiracil hydrochloride at a molar ratio of 1:0.5.

Trifluridine

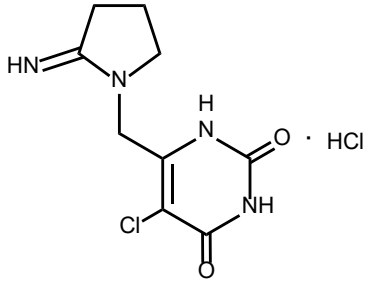
Trifluridine, a nucleoside metabolic inhibitor, is described chemically as 2'-deoxy-5-(trifluoromethyl) uridine and has the following structural formula:



Trifluridine has a molecular formula $C_{10}H_{11}F_3N_2O_5$ and a molecular weight of 296.20. Trifluridine is a white crystalline powder, soluble in water, ethanol, 0.01 mol/L hydrochloric acid, 0.01 mol/L sodium hydroxide solution; freely soluble in methanol, acetone; sparingly soluble in 2-propanol, acetonitrile; slightly soluble in diethyl ether; and very slightly soluble in isopropyl ether.

Tipiracil hydrochloride

Tipiracil hydrochloride, a thymidine phosphorylase inhibitor, is described chemically as 5-chloro-6-[(2-iminopyrrolidin-1-yl)methyl]pyrimidine-2,4-(1*H*,3*H*)-dione monohydrochloride or 2,4(1*H*,3*H*)-Pyrimidinedione, 5-chloro-6-[(2-imino-1-pyrrolidinyl)methyl]-, hydrochloride (1:1) and has the following structural formula:



Tipiracil hydrochloride has a molecular formula $C_9H_{11}ClN_4O_2$•HCl and a molecular weight of 279.12. Tipiracil hydrochloride is a white crystalline powder, soluble in water, 0.01 mol/L hydrochloric acid, and 0.01 mol/L sodium hydroxide; slightly soluble in methanol; very slightly soluble in ethanol; and practically insoluble in acetonitrile, 2-propanol, acetone, diisopropyl ether, and diethyl ether.

LONSURF (trifluridine and tipiracil) tablets for oral use contain 15 mg of trifluridine and 6.14 mg of tipiracil equivalent to 7.065 mg of tipiracil hydrochloride or 20 mg of trifluridine and 8.19 mg of tipiracil equivalent to 9.420 mg of tipiracil hydrochloride.

LONSURF tablets contain the following inactive ingredients: lactose monohydrate, pregelatinized starch, stearic acid, hypromellose, polyethylene glycol, titanium dioxide, ferric oxide, and magnesium stearate. The tablets are imprinted with ink containing shellac, ferric oxide red, ferric oxide yellow, titanium dioxide, FD&C Blue No. 2 Aluminum Lake, carnauba wax, and talc.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

LONSURF consists of a thymidine-based nucleoside analog, trifluridine, and the thymidine phosphorylase inhibitor, tipiracil, at a molar ratio 1:0.5 (weight ratio, 1:0.471). Inclusion of tipiracil increases trifluridine exposure by inhibiting its metabolism by thymidine phosphorylase.

Following uptake into cancer cells, trifluridine is incorporated into DNA, interferes with DNA synthesis and inhibits cell proliferation. Trifluridine/tipiracil demonstrated anti-tumor activity against *KRAS* wild-type and mutant human colorectal cancer xenografts in mice.

12.2 Pharmacodynamics

Cardiac Electrophysiology

LONSURF administered to 42 patients with advanced solid tumors at the recommended dosage had no large effect (i.e. >20 ms) in the mean QTc interval when compared to placebo and no exposure-QT relationship was identified. Two of 42 patients (4.8%) had QTc >500 msec and 2.4% had a QTc increase from baseline >60 msec.

12.3 Pharmacokinetics

After twice daily dosing of LONSURF, systemic exposure (AUC) of trifluridine increased more than dose-proportionally over the dose range of 15 mg/m^2 (0.43 times the recommended dose) to 35 mg/m^2.

The accumulation of trifluridine was 3-fold for $AUC_{0\text{-}12hr}$ and 2-fold for C_{max} at steady state while no accumulation was observed for tipiracil.

Administration of a single dose of LONSURF 35 mg/m^2 increased the mean $AUC_{0\text{-}last}$ of trifluridine by 37-fold and C_{max} by 22-fold with reduced variability compared to administration of a single dose of trifluridine 35 mg/m^2 alone.

Absorption

Following a single oral administration of LONSURF at 35 mg/m^2 in patients with cancer, the mean time to peak plasma concentration (T_{max}) of trifluridine was around 2 hours.

Food Effect

A standardized high-fat, high-calorie meal decreased trifluridine C_{max}, tipiracil C_{max} and AUC by approximately 40%, but did not change trifluridine AUC compared to those in a fasting state in patients with cancer following administration of a single dose of LONSURF 35 mg/m^2.

Distribution

Trifluridine mainly binds to human serum albumin. The in vitro protein binding of trifluridine in human plasma is >96%, independent of drug concentration and presence of tipiracil. Plasma protein binding of tipiracil is below 8%.

Elimination

After administration of LONSURF 35 mg/m^2, the mean elimination half-life ($t_{1/2}$) of trifluridine was 1.4 hours and of tipiracil was 2.1 hours after a single dose. The mean elimination half-life at steady state of trifluridine was 2.1 hours and of tipiracil was 2.4 hours.

Metabolism

Trifluridine and tipiracil are not metabolized by cytochrome P450 (CYP) enzymes. Trifluridine is mainly eliminated by metabolism via thymidine phosphorylase to form an inactive metabolite, 5-(trifluoromethyl) uracil (FTY). No other major metabolites were detected in plasma or urine.

Excretion

After single oral administration of LONSURF (60 mg) with [^{14}C]-trifluridine, the total cumulative excretion of radioactivity was 60% of the administered dose. The majority of recovered radioactivity was eliminated into urine (55% of the dose) as FTY and trifluridine glucuronide isomers within 24 hours and the excretion into feces and expired air was <3% for both. The unchanged trifluridine was <3% of administered dose recovered in the urine and feces.

After single oral administration of LONSURF (60 mg) with [^{14}C]-tipiracil hydrochloride, recovered radioactivity was 77% of the dose, which consisted of 27% urinary excretion and 50% fecal excretion. Tipiracil was the major component and 6-HMU was the major metabolite in urine, and feces.

Specific Populations

Based on the population pharmacokinetic analysis, there is no clinically relevant effect of age, sex, or race (White or Asian) on the pharmacokinetics of trifluridine or tipiracil.

Patients with Renal Impairment

In a dedicated renal impairment study, all patients received LONSURF 35 mg/m^2 twice daily except for patients with severe renal impairment who received 20 mg/m^2 twice daily. Mild renal impairment (CLcr of 60 to 89 mL/min as determined by the Cockcroft-Gault formula) had no clinically important effect on steady-state $AUC_{0\text{-last}}$ of trifluridine and tipiracil. Moderate renal impairment (CLcr of 30 to 59 mL/min) increased steady-state $AUC_{0\text{-last}}$ of trifluridine by 56% and tipiracil by 139% compared to normal renal function (CLcr ≥ 90 mL/min). Severe renal

impairment (CLcr of 15 to 29 mL/min) increased the dose-normalized steady-state $AUC_{0\text{-last}}$ of trifluridine by 140%and tipiracil by 614% compared to normal renal function. The pharmacokinetics of trifluridine and tipiracil have not been studied in patients with end stage renal disease.

Patients with Hepatic Impairment

No clinically important differences in the mean exposures of trifluridine and tipiracil were observed between patients with mild hepatic impairment (total bilirubin ≤ ULN and AST > ULN or total bilirubin <1 to 1.5 times ULN and any AST) to moderate hepatic impairment (total bilirubin >1.5 to 3 times ULN and any AST) and patients with normal hepatic function (total bilirubin and AST ≤ ULN); however, 5 of 6 patients with moderate hepatic impairment experienced Grade 3 or 4 increased bilirubin levels. The pharmacokinetics of trifluridine and tipiracil have not been studied in patients with severe hepatic impairment *[see Dosage Modifications (2.2), Use in Specific Populations (8.6)]*.

Drug Interaction Studies

In vitro studies indicated that trifluridine, tipiracil, and FTY did not inhibit the CYP enzymes and had no inductive effect on CYP1A2, CYP2B6, or CYP3A4/5.

In vitro studies indicated that trifluridine was not an inhibitor of or substrate for human uptake and efflux transporters.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term studies evaluating the carcinogenic potential of trifluridine/tipiracil in animals have been performed. Trifluridine/tipiracil was genotoxic in a reverse mutation test in bacteria, a chromosomal aberration test in mammalian-cultured cells, and a micronucleus test in mice.

Animal studies did not indicate an effect of trifluridine/tipiracil on male fertility in rats. Dose-related increases in the corpus luteum count and implanted embryo count were observed, but female fertility was not affected.

14 CLINICAL STUDIES

14.1 Metastatic Colorectal Cancer

The efficacy of LONSURF was evaluated in RECOURSE (NCT01607957), an international, randomized, double-blind, placebo-controlled study conducted in patients with previously treated metastatic colorectal cancer (mCRC). Key eligibility criteria included prior treatment with at least 2 lines of standard chemotherapy for metastatic CRC, ECOG performance status (PS) 0-1, absence of brain metastasis, and absence of ascites requiring drainage in the past four weeks. Patients were randomized 2:1 to receive LONSURF 35 mg/m^2 or matching placebo orally twice daily after meals on Days 1-5 and 8-12 of each 28-day cycle until disease progression or unacceptable toxicity. Randomization was stratified by KRAS status (wild-type vs. mutant), time since diagnosis of first metastasis (<18 months vs. ≥ 18 months), and region (Japan vs. US,

Europe and Australia). The major efficacy outcome measure was overall survival (OS) and an additional efficacy outcome measure was progression-free survival (PFS).

A total of 800 patients were randomized to LONSURF (N=534) with best supportive care (BSC) or matching placebo (N=266) plus BSC. The median age was 63 years, 61% were male, 58% and 35% were White and Asian respectively, and all patients had baseline ECOG PS of 0 or 1. The primary site of disease was colon (62%) or rectum (38%). KRAS status was wild-type (49%) or mutant (51%) at study entry. All patients received prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy. All but one patient received bevacizumab and all but two patients with KRAS wild-type tumors received panitumumab or cetuximab.

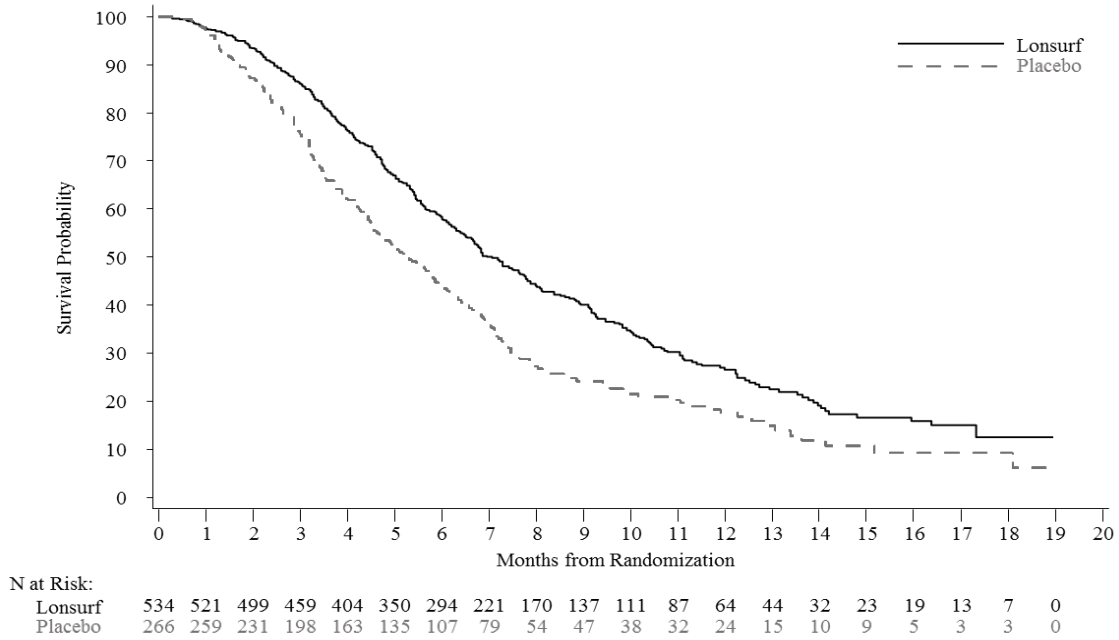
Efficacy results are summarized in Table 7 and Figure 1.

Table 7 Efficacy Results from RECOURSE

	LONSURF (N=534)	**Placebo (N=266)**
Overall Survival		
Number of deaths, N (%)	364 (68)	210 (79)
Median OS (months)[a] (95% CI)[b]	7.1 (6.5, 7.8)	5.3 (4.6, 6.0)
Hazard ratio (95% CI)	0.68 (0.58, 0.81)	
p-value[c]	<0.001	
Progression-Free Survival		
Number of events, N (%)	472 (88)	251 (94)
Hazard ratio (95% CI)	0.47 (0.40, 0.55)	
p-value[c]	<0.001	

[a] Kaplan-Meier estimates
[b] Methodology of Brookmeyer and Crowley
[c] Stratified log-rank test (strata: KRAS status, time since diagnosis of first metastasis, region), 2-sided

Figure 1 Kaplan-Meier Curves of Overall Survival in RECOURSE



14.2 Metastatic Gastric Cancer

The efficacy of LONSURF was evaluated in TAGS (NCT02500043), an international, randomized, double-blind, placebo-controlled study in patients with metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma previously treated with at least 2 prior regimens for advanced disease. Previous treatments must have included a fluoropyrimidine, a platinum, and either a taxane or irinotecan. Patients with HER2/neu-positive tumors must have received prior HER2/neu-targeted therapy, if available. Adjuvant chemotherapy could be counted as one prior regimen in patients who had recurrence during or within 6 months of completion of the adjuvant chemotherapy. Other key eligibility criteria included ECOG performance status (PS) 0 or 1. Patients were randomized 2:1 to receive LONSURF 35 mg/m^2 orally twice daily on Days 1-5 and 8-12 of each 28-day cycle with best supportive care (BSC) or matching placebo with BSC until disease progression or unacceptable toxicity. Randomization was stratified by ECOG PS at baseline (0 vs. 1), prior ramucirumab (yes vs. no), and geographic region (Japan vs. rest of world). The major efficacy outcome measure was OS and an additional outcome measure was PFS.

A total of 507 patients were randomized to LONSURF (N=337) or placebo (N=170). The median age was 63 years, 73% were male, 70% and 16% were White and Asian respectively, and 38% had a baseline ECOG PS of 0. Seventy-one percent of patients had gastric tumors, 29% had GEJ tumors, and two patients had gastric/GEJ tumors. All patients received platinum-based chemotherapy, 99% received fluoropyrimidine-based therapy, 91% received a taxane, 55% received irinotecan, and 33% received ramucirumab. The HER2 status was negative in 62%, positive in 19%, and unknown in 20% of patients. Among the 94 patients with HER2 positive tumors, 89% received prior anti-HER2 therapy.

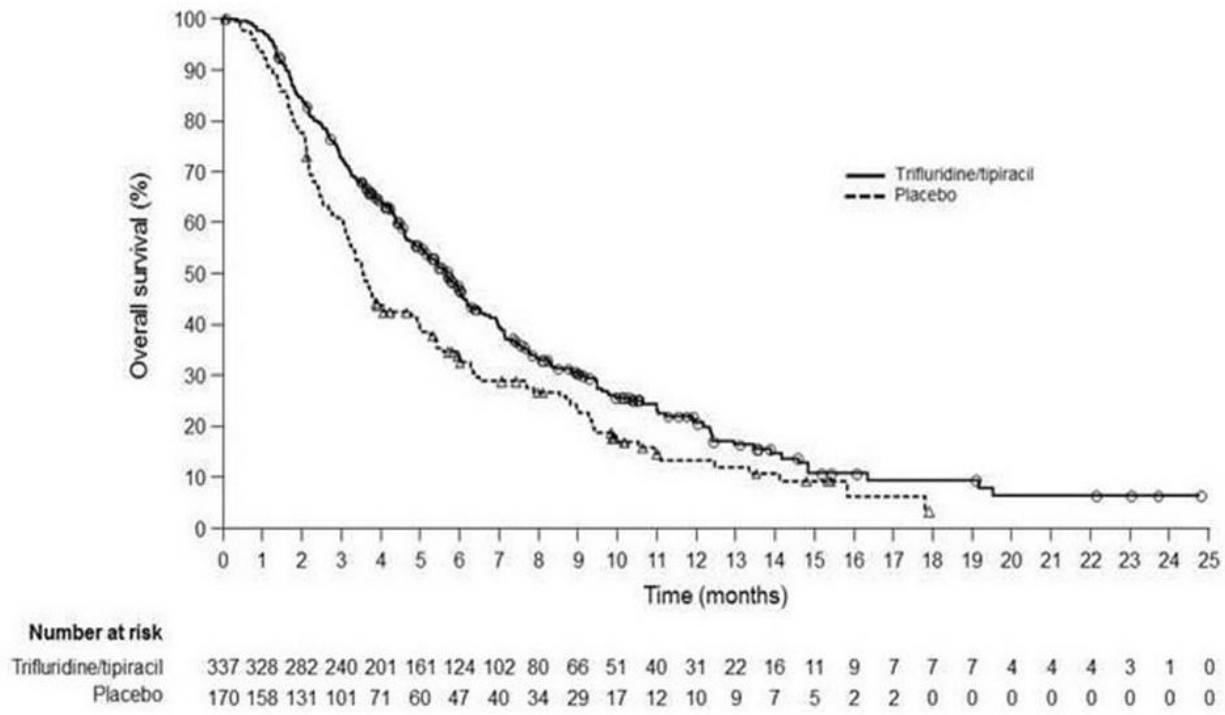
Efficacy results are summarized in Table 8 and Figure 2.

Table 8 Efficacy Results from TAGS

	LONSURF (N=337)	Placebo (N=170)
Overall Survival		
Number of deaths, N (%)	244 (72)	140 (82)
Median OS (months)[a] (95% CI)[b]	5.7 (4.8, 6.2)	3.6 (3.1, 4.1)
Hazard ratio (95% CI)	0.69 (0.56, 0.85)	
p-value[c]	0.0006	
Progression-Free Survival		
Number of events, N (%)	287 (85)	156 (92)
Hazard ratio (95% CI)	0.56 (0.46, 0.68)	
p-value[c]	<0.0001	

[a] Kaplan-Meier estimates
[b] Methodology of Brookmeyer and Crowley
[c] Stratified log-rank test (strata: ECOG PS, prior ramucirumab treatment, region), 2-sided

Figure 2 Kaplan-Meier Curves of Overall Survival in TAGS



15 REFERENCES

1. "OSHA Hazardous Drugs". OSHA. http://www.osha.gov/SLTC/hazardousdrugs/index.html

16 HOW SUPPLIED/STORAGE AND HANDLING

LONSURF 15 mg/6.14 mg tablets are supplied as white, biconvex, round, film-coated tablet, imprinted with '15' on one side, and '102' and '15 mg' on the other side, in gray ink. The tablets are packaged in HDPE bottles with child resistant closures in the following presentations:

- 20 count: NDC 64842-1025-1
- 40 count: NDC 64842-1025-2
- 60 count: NDC 64842-1025-3

LONSURF 20 mg/8.19 mg tablets are supplied as pale red, biconvex, round, film-coated tablet, imprinted with '20' on one side, and '102' and '20 mg' on the other side, in gray ink. The tablets are packaged in HDPE bottles with child resistant closures in the following presentations:

- 20 count: NDC 64842-1020-1
- 40 count: NDC 64842-1020-2
- 60 count: NDC 64842-1020-3

Store at 20°C to 25°C (68°F to 77°F); excursions are permitted from 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature].

LONSURF is a cytotoxic drug. Follow applicable special handling and disposal procedures.[1]

If stored outside of original bottle, discard after 30 days.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Severe Myelosuppression

Advise patients to immediately contact their healthcare provider if they experience signs or symptoms of infection and advise patients to keep all appointments for blood tests *[see Warnings and Precautions (5.1)]*.

Gastrointestinal Toxicity

Advise patients to contact their healthcare provider for severe or persistent nausea, vomiting, diarrhea, or abdominal pain *[see Adverse Reactions (6.1)]*.

Administration Instructions

Advise patients that LONSURF is available in two strengths and they may receive both strength tablets to provide the prescribed dosage.

Advise patients to take LONSURF with food *[see Dosage and Administration (2.1)]*.

Advise patients that anyone else who handles their medication should wear gloves *[*see *References (15)]*.

Embryo-Fetal Toxicity

Advise pregnant women and females of reproductive potential of the potential risk to the fetus. Advise females to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.2), Use in Specific Populations (8.3)]*.

Advise female patients of reproductive potential to use effective contraception during treatment with LONSURF and for at least 6 months after the final dose *[see Warnings and Precautions (5.2), Use in Specific Populations (8.3)]*.

Advise males with female partners of reproductive potential to use condoms during treatment with LONSURF and for at least 3 months after the final dose *[see Use in Specific Populations (8.3), Nonclinical Toxicology (13.1)]*.

Lactation

Advise women not to breastfeed during treatment with LONSURF and for 1 day following the final dose *[see Use in Specific Populations (8.2)]*.

Manufactured by: Taiho Pharmaceutical Co., Ltd., Japan
Manufactured for: Taiho Oncology, Inc., Princeton, NJ 08540 USA

LONSURF is a registered trademark of Taiho Pharmaceutical Co., Ltd used under license by Taiho Oncology, Inc.

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EXKIVITY™ (mobocertinib)
ACCESS GUIDE

INDICATION

EXKIVITY is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy.

This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

IMPORTANT SAFETY INFORMATION

WARNING: QTc PROLONGATION and TORSADES DE POINTES

See full prescribing information for complete boxed warning.

- **EXKIVITY can cause life-threatening heart rate–corrected QT (QTc) prolongation, including Torsades de Pointes, which can be fatal, and requires monitoring of QTc and electrolytes at baseline and periodically during treatment. Increase monitoring frequency in patients with risk factors for QTc prolongation.**
- **Avoid use of concomitant drugs which are known to prolong the QTc interval and use of strong or moderate CYP3A inhibitors with EXKIVITY, which may further prolong the QTc.**
- **Withhold, reduce the dose, or permanently discontinue EXKIVITY based on the severity of QTc prolongation.**

Please see Important Safety Information on pages 4 and 5 and accompanying full Prescribing Information, including Boxed Warning.

Please see page 3 for information about Takeda Oncology Here2Assist™.

EXKIVITY™
mobocertinib
40 mg capsules

Distribution Details for EXKIVITY™ (mobocertinib)

Product name	EXKIVITY™ (mobocertinib) capsules, for oral use
Distributed and marketed by	Takeda Pharmaceuticals U.S.A., Inc.
Storage and handling	Store at 20°C to 25°C (68°F to 77°F); excursions permitted from 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].
Recommended dosing	The recommended dosage of EXKIVITY is 160 mg orally once daily until disease progression or unacceptable toxicity.

How supplied

Strength	Count	NDC
40 mg	Bottle of 120 capsules	63020-040-12

Capsules: white, size 2, imprinted with "MB788" on the cap and "40mg" on the body in black ink.

Ordering

EXKIVITY can be ordered from one of the following Specialty Pharmacies:

Biologics
1-800-850-4306
biologics.mckesson.com

Onco360
1-877-662-6633
onco360.com

EXKIVITY must be filled through one of these in-network specialty pharmacies. Sending an EXKIVITY prescription to an alternate pharmacy may result in delay or nonfulfillment of the prescription.

EXKIVITY may be purchased directly by qualified entities* from the following distribution partners:

ASD Healthcare
1-800-746-6273
www.asdhealthcare.com

Cardinal
1-877-453-3972
www.cardinalhealth.com

McKesson Specialty Care
1-800-482-6700
www.mckesson.com

McKesson Plasma and Biologics
1-877-625-2566
www.mckesson.com

Oncology Supply
1-800-633-7555
www.oncologysupply.com

NDC, National Drug Code.

*Qualified entities for direct purchase include hospitals, physician practices, and institutions that have been licensed by a state agency to dispense pharmaceutical products to appropriate patients, excluding specialty pharmacy providers and retail pharmacies. Eligible government entities include the Department of Defense, Department of Veterans Affairs, and 340B covered entities.

Please see Important Safety Information on pages 4 and 5 and accompanying full Prescribing Information, including Boxed Warning.

EXKIVITY™
mobocertinib
40 mg capsules

Takeda Oncology Here2Assist

We're here to help your patients with their coverage, financial, and educational resource needs

Takeda Oncology Here2Assist™:

- **Works** with your patients' insurance company to help get your patient started on their medication
- **Identifies** available financial assistance that may be right for your patients
- **May help** eligible patients get started on treatment in the event of an insurance delay
- **Identifies** specialty pharmacies to help fill and ship your patients' prescriptions appropriately
- **Conducts** regular follow-up calls to patients
- **Sends** text message status updates and reminders to patients*
- **Connects** your patients with nurse navigators to support their product education journey†

For more information about patient access support and financial assistance that your patients may qualify for, call us at 1-844-817-6468, Option 2. Let's Talk. We're available Monday-Friday, 8AM–8PM ET, or visit us at www.Here2Assist.com/hcp to learn more.

The Takeda Oncology Here2Assist RapidStart Program

If your patient experiences a delay in insurance coverage determination of at least 5 business days, your patient may be eligible to receive a 1-month supply of medication at no cost to them. Terms and Conditions apply.‡

Visit www.Here2Assist.com to download the appropriate RapidStart Request Form.

Takeda Oncology Co-Pay Assistance Program

For patients who are commercially insured and concerned about their out-of-pocket costs, the Takeda Oncology Co-Pay Assistance Program§ may be able to help.

Your patient could pay as little as $0 per prescription. Terms and Conditions apply.§

Visit www.TakedaOncologyCopay.com or call to speak with a Takeda Oncology Here2Assist case manager at 1-844-817-6468, Option 2, Monday-Friday, 8AM–8PM ET.

Takeda Oncology Patient Assistance Program

If your patient is uninsured or the prescribed medication is not covered, the patient may be eligible to receive their Takeda Oncology medication at no cost through our Patient Assistance Program.¶

Visit www.Here2Assist.com to download the Patient Assistance Program Application.

*Patients will need to enroll in the texting program to receive text messages.

†For EXKIVITY patients only.

‡The RapidStart Program provides a 1-month supply of treatment of the prescribed Takeda Oncology medication at no charge for eligible patients new to therapy experiencing a delay in insurance coverage determination of at least 5 business days. There is no purchase obligation by virtue of a patient's participation in the RapidStart Program. Patients must have an on-label, valid prescription for the Takeda Oncology medication, and a medical necessity for being prescribed the Takeda Oncology medication. Patients must be enrolled in the Takeda Oncology Here2Assist Program to qualify. Free product for the RapidStart Program will only be available through the RapidStart Program noncommercial specialty pharmacy. A delay in coverage determination of at least 5 days is required for patients to be eligible for the RapidStart Program. The program may not be combined with any other offer and is not available to patients whose insurers have made a final determination to deny the patient coverage for the prescribed Takeda Oncology medication. Takeda reserves the right to change or end the program at any time. Benefits provided under the program are not transferable.

§Takeda Oncology Co-Pay Assistance Program Terms and Conditions: This offer cannot be used if you are a beneficiary of, or any part of your prescription is covered or reimbursed by: (1) any federal or state healthcare program (Medicare, Medicaid, TRICARE, Veterans Administration, Department of Defense, etc.), including a state or territory pharmaceutical assistance program, (2) the Medicare Prescription Drug Program (Part D), or if you are currently in the coverage gap, Medicare Advantage Plans, Medicaid Managed Care or Alternative Benefit Plans under the Affordable Care Act, or Medigap, or (3) insurance that is paying the entire cost of the prescription. Patients must be at least 18 years old and be a resident of the United States or a US Territory.

You must meet Eligibility Requirements. You agree to report your use of this offer to any third party that reimburses you or pays for any part of the prescription price. Use of this offer is confirmation that you are permitted, under the terms and conditions of the health benefit plan(s) covering your prescription, to take advantage of co-pay assistance programs. You additionally agree that you will not submit the cost of any portion of the product dispensed pursuant to this offer to a federal or state healthcare program (Medicare, Medicaid, TRICARE, Veterans Administration, Department of Defense, etc.), for purposes of counting it toward your out-of-pocket expenses, and to notify Takeda Oncology Here2Assist if you become eligible for a federal or state healthcare program. This assistance program may cover out-of-pocket expenses for your Takeda Oncology medication up to a maximum of $25,000 annually. Your co-pay card can be renewed every 12 months, subject to continued eligibility. This offer is not valid with any other program, discount, or offer involving your prescribed Takeda Oncology medication. This offer may be rescinded, revoked, or amended without notice. No reproductions. This offer is void where prohibited by law, taxed, or restricted. Limit one offer per purchase. Cash value of 1/100 of 1¢. For questions about this offer, please contact the Takeda Oncology Co-Pay Assistance Program, a patient support service of Takeda Oncology Here2Assist, at 1-844-817-6468, Option 2, Monday-Friday, 8AM–8PM ET.

¶To be eligible for the Patient Assistance Program, patients must meet certain financial and insurance coverage criteria. A Patient Assistance Program Application must be submitted in order to confirm patient eligibility.

IMPORTANT SAFETY INFORMATION (CONT'D)

WARNINGS AND PRECAUTIONS

QTc Prolongation and Torsades de Pointes

EXKIVITY can cause life-threatening heart rate–corrected QT (QTc) prolongation, including Torsades de Pointes, which can be fatal. In the 250-patient subset of the pooled EXKIVITY safety population who had scheduled and unscheduled electrocardiograms (ECGs), 1.2% of patients had a QTc interval >500 msec and 11% of patients had a change-from-baseline QTc interval >60 msec. Grade 4 Torsades de Pointes occurred in 1 patient (0.4%). Clinical trials of EXKIVITY did not enroll patients with baseline QTc greater than 470 msec.

Assess QTc and electrolytes at baseline and correct abnormalities in sodium, potassium, calcium, and magnesium prior to initiating EXKIVITY. Monitor QTc and electrolytes periodically during treatment. Increase monitoring frequency in patients with risk factors for QTc prolongation, such as patients with congenital long QT syndrome, heart disease, or electrolyte abnormalities. Avoid use of concomitant drugs which are known to prolong the QTc interval. Avoid concomitant use of strong or moderate CYP3A inhibitors with EXKIVITY, which may further prolong the QTc. Withhold, reduce the dose, or permanently discontinue EXKIVITY based on the severity of the QTc prolongation.

Interstitial Lung Disease (ILD)/Pneumonitis

EXKIVITY can cause ILD/pneumonitis, which can be fatal. In the pooled EXKIVITY safety population, ILD/pneumonitis occurred in 4.3% of patients including 0.8% Grade 3 events and 1.2% fatal events. Monitor patients for new or worsening pulmonary symptoms indicative of ILD/pneumonitis. Immediately withhold EXKIVITY in patients with suspected ILD/pneumonitis and permanently discontinue EXKIVITY if ILD/pneumonitis is confirmed.

Cardiac Toxicity

EXKIVITY can cause cardiac toxicity (including decreased ejection fraction, cardiomyopathy, and congestive heart failure) resulting in heart failure, which can be fatal. In the pooled EXKIVITY safety population, heart failure occurred in 2.7% of patients including 1.2% Grade 3 reactions, 0.4% Grade 4 reactions, and one (0.4%) fatal case of heart failure.

EXKIVITY can cause QTc prolongation resulting in Torsades de Pointes. Atrial fibrillation (1.6%), ventricular tachycardia (0.4%), first-degree atrioventricular block (0.4%), second-degree atrioventricular block (0.4%), left bundle branch block (0.4%), supraventricular extrasystoles (0.4%), and ventricular extrasystoles (0.4%) also occurred in patients receiving EXKIVITY. Monitor cardiac function, including assessment of left ventricular ejection fraction at baseline and during treatment. Withhold, reduce the dose, or permanently discontinue EXKIVITY based on the severity.

Diarrhea

EXKIVITY can cause diarrhea, which can be severe. In the pooled EXKIVITY safety population, diarrhea occurred in 93% of patients, including 20% Grade 3 and 0.4% Grade 4. The median time to first onset of diarrhea was 5 days, but diarrhea has occurred within 24 hours after administration of EXKIVITY. In the 48% of patients whose diarrhea resolved, the median time to resolution was 3 days. Diarrhea may lead to dehydration or electrolyte imbalance, with or without renal impairment. Treat diarrhea promptly.

Advise patients to start an antidiarrheal agent (eg, loperamide) at first sign of diarrhea or increased bowel movement frequency and to increase fluid and electrolyte intake. Monitor electrolytes and withhold, reduce the dose or permanently discontinue EXKIVITY based on the severity.

Embryo-Fetal Toxicity

Based on findings from animal studies and its mechanism of action, EXKIVITY can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective nonhormonal contraception during treatment with EXKIVITY and for 1 month after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with EXKIVITY and for 1 week after the last dose of EXKIVITY.

Please see Important Safety Information on pages 4 and 5 and accompanying full Prescribing Information, including Boxed Warning.

EXKIVITY™
mobocertinib
40 mg capsules

IMPORTANT SAFETY INFORMATION (CONT'D)

ADVERSE REACTIONS

The most common (>20%) adverse reactions are diarrhea, rash, nausea, stomatitis, vomiting, decreased appetite, paronychia, fatigue, dry skin, and musculoskeletal pain. The most common (≥2%) Grade 3 or 4 laboratory abnormalities were decreased lymphocytes, increased amylase, increased lipase, decreased potassium, decreased hemoglobin, increased creatinine, and decreased magnesium.

DRUG INTERACTIONS

CYP3A Inhibitors

Coadministration of EXKIVITY with strong or moderate CYP3A inhibitors increased mobocertinib plasma concentrations, which may increase the risk of adverse reactions, including QTc interval prolongation. Avoid concomitant use of strong or moderate CYP3A inhibitors with EXKIVITY. If concomitant use of moderate CYP3A inhibitors cannot be avoided, reduce the EXKIVITY dose and monitor the QTc interval more frequently with ECGs.

CYP3A Inducers

Coadministration of EXKIVITY with strong or moderate CYP3A inducers decreased mobocertinib plasma concentrations, which may reduce EXKIVITY antitumor activity. Avoid concomitant use of strong or moderate CYP3A inducers with EXKIVITY.

CYP3A Substrates

Coadministration of EXKIVITY with CYP3A substrates may decrease plasma concentrations of CYP3A substrates, which may reduce the efficacy of these substrates. Avoid concomitant use of hormonal contraceptives with EXKIVITY. Avoid concomitant use of EXKIVITY with other CYP3A substrates where minimal concentration changes may lead to serious therapeutic failures. If concomitant use is unavoidable, increase the CYP3A substrate dosage in accordance with the approved product Prescribing Information.

Prolonged QTc Interval

EXKIVITY can cause QTc interval prolongation. Coadministration of EXKIVITY with drugs known to prolong the QTc interval may increase the risk of QTc interval prolongation. Avoid concomitant use of other medications known to prolong the QTc interval with EXKIVITY. If concomitant use is unavoidable, monitor the QTc interval more frequently with ECGs.

USE IN SPECIFIC POPULATIONS

Pregnancy

Based on findings from animal studies and its mechanism of action, EXKIVITY can cause fetal harm when administered to a pregnant woman. There are no available data on EXKIVITY use in pregnant women. Advise pregnant women of the potential risk to a fetus.

Females and Males of Reproductive Potential

Verify pregnancy status in females of reproductive potential prior to initiating EXKIVITY. Advise females of reproductive potential to use effective nonhormonal contraception during treatment with EXKIVITY and for 1 month after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with EXKIVITY and for 1 week after the last dose.

Lactation

There are no data on the presence of mobocertinib or its metabolites in human milk or their effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with EXKIVITY and for 1 week after the last dose.

To report SUSPECTED ADVERSE REACTIONS, contact Takeda Pharmaceuticals U.S.A., Inc. at **1-844-217-6468** or the FDA at **1-800-FDA-1088** or **www.fda.gov/medwatch**.

Please see full Prescribing Information, including Boxed Warning.

To learn more about EXKIVITY, please visit EXKIVITYhcp.com.

Reference: Exkivity. Prescribing Information. Takeda Pharmaceuticals U.S.A., Inc.; 2021. Accessed September 15, 2021. https://takeda.info/Exkivity-Prescribing-Information

EXKIVITY™
mobocertinib
40 mg capsules

Takeda | ONCOLOGY

EXKIVITY™
mobocertinib
40 mg capsules

Takeda Oncology
Here2Assist

Supporting your patients is our specialty

Phyllis
Takeda Oncology
Here2Assist™ patient

We're here to help with coverage, financial, and educational resource needs

Personalized support for patients prescribed Takeda Oncology products, including:

Phyllis
Takeda Oncology
Here2Assist patient

ALUNBRIG®
BRIGATINIB
180mg | 90mg | 30mg
TABLETS

EXKIVITY™
mobocertinib
40 mg capsules

Please see full Prescribing Information, including Boxed Warning.

ICLUSIG®
(ponatinib) tablets
45mg / 30mg / 15mg / 10mg

Please see full Prescribing Information, including Boxed Warning.

NINLARO®
(ixazomib) capsules
4mg | 3mg | 2.3mg

Comprehensive support

AS OUR PROGRAMS CONTINUOUSLY EVOLVE TO ADAPT TO YOUR PATIENTS' NEEDS, TAKEDA ONCOLOGY HERE2ASSIST™:

- Works with your patients' insurance company to help get your patient started on their medication
- Identifies available financial assistance that may be right for your patients
- May help eligible patients get started on treatment in the event of an insurance delay
- Identifies specialty pharmacies to help fill and ship your patients' prescriptions appropriately
- Conducts regular follow-up calls to patients
- Sends text message status updates and reminders to patients*

*Patients will need to enroll in the texting program to receive text messages.

Let's Talk

BY PHONE

Speak with a Takeda Oncology Here2Assist case manager at 1-844-817-6468, Option 2, Monday-Friday, 8AM-8PM ET

BY FAX

1-844-269-3038

ONLINE

www.Here2Assist.com

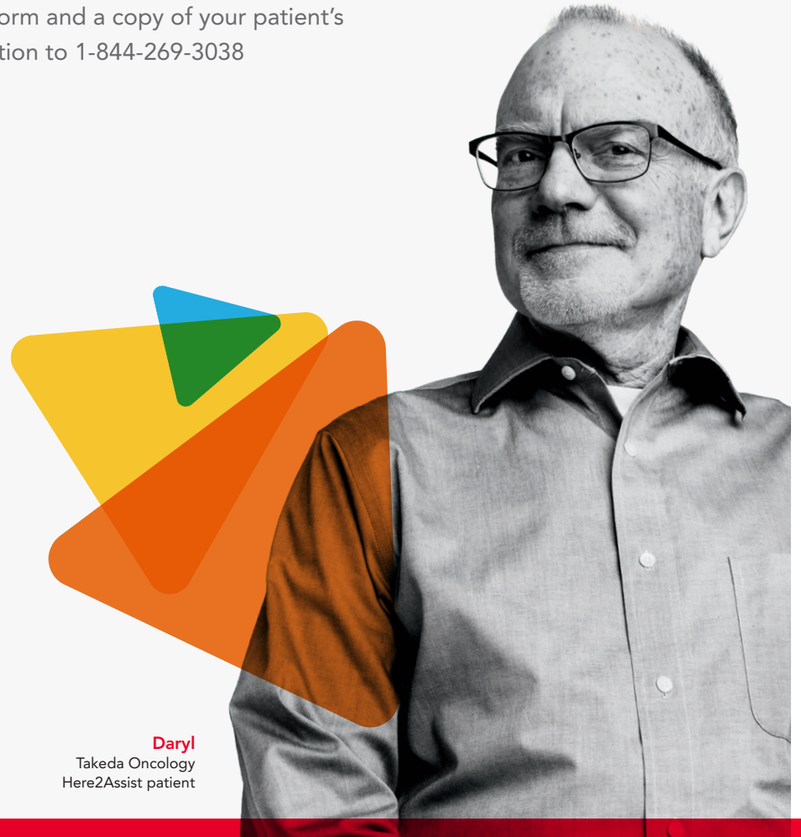
Takeda | ONCOLOGY

Simple enrollment

1. DOWNLOAD
and print the Takeda Oncology Here2Assist™ Enrollment Form from **www.Here2Assist.com**

2. COMPLETE
and sign the enrollment form together with your patient

3. FAX
the completed enrollment form and a copy of your patient's insurance card and prescription to 1-844-269-3038



Daryl
Takeda Oncology
Here2Assist patient

Access support

Our case managers are here to help your patients get access to their prescribed Takeda Oncology treatment through the following:

BENEFITS VERIFICATION

Assisting you in researching coverage guidelines for the prescribed medication on behalf of your patient, using information provided during the enrollment process to identify payer policies that require verification, notifying you and your office of a verification outcome or status, and referring prescriptions to your preferred specialty pharmacy or determining one in your patients' payer network

PRIOR AUTHORIZATIONS

Supplying a summary of process and submission requirements,* sending renewal reminders, and communicating status and expirations of prior authorizations to your office

PAYER DENIALS

Providing support by explaining reasons for the denial and the process for appeal*

- To download a Sample Letter of Medical Necessity or Sample Letter of Appeal, visit **www.Here2Assist.com**

Questions about enrollment or access support?

Visit us at www.Here2Assist.com or call us at 1-844-817-6468, Option 2.
Let's Talk. We're available Monday-Friday, 8AM-8PM ET.

*Takeda Oncology Here2Assist does not complete forms, file claims, or appeal claims for callers. It cannot guarantee success in overturning a payer denial.

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Access support (continued)

If your patient experiences a delay in insurance coverage determination of at least 5 days, your patient may be eligible to receive a 1-month supply of Takeda Oncology medication at no cost to them. Terms and Conditions apply.*

ENROLL YOUR PATIENTS IN THE RAPIDSTART PROGRAM*

1. ENSURE
your patient has a completed Takeda Oncology Here2Assist™ Enrollment Form on file

2. VISIT
www.Here2Assist.com to download the appropriate RapidStart Request Form

3. WORK
with your patient to complete the RapidStart Request Form

4. FAX
the completed RapidStart Request Form, along with an on-label prescription for your patient's medication, to 1-844-269-3038

RapidStart Program eligibility to be determined upon enrollment.

Speak with your patient's case manager for more details.

*The RapidStart Program provides a 1-month supply of treatment of the prescribed Takeda Oncology medication at no charge for eligible patients new to therapy experiencing a delay in insurance coverage determination of at least 5 business days. There is no purchase obligation by virtue of a patient's participation in the RapidStart Program. Patients must have an on-label, valid prescription for the Takeda Oncology medication, and a medical necessity for being prescribed the Takeda Oncology medication. Patients must be enrolled in the Takeda Oncology Here2Assist Program to qualify. Free product for the RapidStart Program will only be available through the RapidStart Program noncommercial specialty pharmacy. A delay in coverage determination of at least 5 days is required for patients to be eligible for the RapidStart Program. The program may not be combined with any other offer and is not available to patients whose insurers have made a final determination to deny the patient coverage for the prescribed Takeda Oncology medication. Takeda reserves the right to change or end the program at any time. Benefits provided under the program are not transferable.

Takeda Oncology Here2Assist works with you to help get Takeda Oncology medication to your patient.

SPECIALTY PHARMACY REFERRAL AND COORDINATION

Our case managers can assist in identifying specialty pharmacies to help fill and ship your patients' prescriptions appropriately.

IN-OFFICE DISPENSING†

In-office dispensing may be available for some medications. To arrange in-office dispensing, please contact Takeda Oncology Here2Assist directly at 1-844-817-6468, Option 5, Monday-Friday, 8AM-8PM ET.

Questions about access support?

Visit us at www.Here2Assist.com or call us at 1-844-817-6468, Option 2.
Let's Talk. We're available Monday-Friday, 8AM-8PM ET.

†May not apply to all products.

Hans
Takeda Oncology
Here2Assist patient

Takeda | ONCOLOGY

Financial assistance

TAKEDA ONCOLOGY CO-PAY ASSISTANCE PROGRAM

For patients who are commercially insured and concerned about their out-of-pocket costs, the Takeda Oncology Co-Pay Assistance Program* may be able to help.

HELP YOUR PATIENTS ENROLL TODAY

Visit **www.Here2Assist.com** or call to speak with a Takeda Oncology Here2Assist™ case manager at 1-844-817-6468, Option 2, Monday-Friday, 8AM-8PM ET.

Your patient could pay as little as $0 per prescription.

Terms and Conditions apply*

*Takeda Oncology Co-Pay Assistance Program Terms and Conditions: This offer cannot be used if you are a beneficiary of, or any part of your prescription is covered or reimbursed by: (1) any federal or state healthcare program (Medicare, Medicaid, TRICARE, Veterans Administration, Department of Defense, etc.), including a state or territory pharmaceutical assistance program, (2) the Medicare Prescription Drug Program (Part D), or if you are currently in the coverage gap, Medicare Advantage Plans, Medicaid Managed Care or Alternative Benefit Plans under the Affordable Care Act, or Medigap, or (3) insurance that is paying the entire cost of the prescription. Patients must be at least 18 years old.

You must meet Eligibility Requirements. You agree to report your use of this offer to any third party that reimburses you or pays for any part of the prescription price. Use of this offer is confirmation that you are permitted, under the terms and conditions of the health benefit plan(s) covering your prescription, to take advantage of co-pay assistance programs. You additionally agree that you will not submit the cost of any portion of the product dispensed pursuant to this offer to a federal or state healthcare program (Medicare, Medicaid, TRICARE, Veterans Administration, Department of Defense, etc.), for purposes of counting it toward your out-of-pocket expenses, and to notify Takeda Oncology Here2Assist if you become eligible for a federal or state healthcare program. This assistance program covers out-of-pocket expenses greater than $0 per monthly prescription. Maximum $25,000 annually. Your co-pay card can be renewed every 12 months, subject to continued eligibility. This offer is not valid with any other program, discount, or offer involving your prescribed Takeda Oncology medication. This offer may be rescinded, revoked, or amended without notice. No reproductions. This offer is void where prohibited by law, taxed, or restricted. Limit one offer per purchase. Cash value of 1/100 of 1¢. For questions about this offer, please contact the Takeda Oncology Co-Pay Assistance Program, a patient support service of Takeda Oncology Here2Assist, at 1-844-817-6468, Option 2, Monday-Friday, 8AM-8PM ET.

TAKEDA ONCOLOGY PATIENT ASSISTANCE PROGRAM

If your patient is uninsured or the prescribed Takeda Oncology medication is not covered, the patient may be eligible to receive medication at no cost through our Patient Assistance Program (PAP).†

HELP YOUR PATIENTS APPLY FOR PAP TODAY

- Visit **www.Here2Assist.com** to download the Takeda Oncology Patient Assistance Program Application
- Work with your patient to complete and submit the application with a valid prescription for his or her medication

If your patient qualifies, he or she may be enrolled for up to 1 year. Upon enrollment, a Takeda Oncology Here2Assist case manager will notify you and your patient. A 1-month supply of medication will be delivered to your patient at no cost to them. Each month, a Takeda Oncology Here2Assist case manager will confirm with you and your patient that he or she is still being treated and is eligible to receive another month's supply of medication.

TAKEDA ONCOLOGY HERE2ASSIST NOTES:

Looking for more?

Visit us at www.Here2Assist.com or call us at 1-844-817-6468, Option 2.

Let's Talk. We're available Monday-Friday, 8AM-8PM ET.

†To be eligible for the Patient Assistance Program, patients must meet certain financial and insurance coverage criteria. A Patient Assistance Program Application must be submitted in order to confirm patient eligibility.

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Helpful resources

TAKEDA ONCOLOGY HERE2ASSIST™ CASE MANAGERS CAN PROVIDE INFORMATION ABOUT AVAILABLE SUPPORT SERVICES FOR PATIENTS INCLUDING:

- Financial assistance for eligible patients
- Regular follow-up calls
- Connects your patients with nurse navigators to support their product education journey*

*For EXKIVITY™ (mobocertinib) patients only.

Questions about additional resources?

Visit us at www.Here2Assist.com or call us at 1-844-817-6468, Option 2.

Let's Talk. We're available Monday-Friday, 8AM-8PM ET.

Takeda | ONCOLOGY

Talk to your patients about Takeda Oncology Here2Assist™ today

A GUIDE TO TAKEDA ONCOLOGY HERE2ASSIST

Visit **www.Here2Assist.com** to access your comprehensive patient support services.

ACCESS SUPPORT

Connect your patients to personalized support

- ☐ Visit **www.Here2Assist.com** together with your patient to download, complete, and submit the enrollment form
- ☐ Once enrolled, our Takeda Oncology Here2Assist case managers can assist your patients with navigating access support
- ☐ Case managers can also help eligible patients get started on their Takeda Oncology therapy in the event of an insurance delay

FINANCIAL SUPPORT

Assist your patients with financial assistance programs

- ☐ Learn about our Takeda Oncology Co-Pay Assistance Program,* including a link to the enrollment website and downloadable enrollment forms
- ☐ Find out more about our Takeda Oncology Patient Assistance Program,* including downloadable enrollment forms

HELPFUL RESOURCES

Provide your patients with information about additional resources

- ☐ Learn about general medical terms with our Guide to Understanding Medication Coverage

*Terms and Conditions apply.

Takeda | ONCOLOGY

Takeda Oncology Here2Assist

Enrollment is simple

Takeda Oncology Here2Assist™ can be your patients' connection to personalized support

1. DOWNLOAD
and print the Takeda Oncology Here2Assist Enrollment Form from **www.Here2Assist.com**

2. COMPLETE
and sign the enrollment form together with your patient

3. FAX
the completed enrollment form and a copy of your patient's insurance card and prescription to 1-844-269-3038

Still have questions about Takeda Oncology Here2Assist?

Visit us at www.Here2Assist.com or call us at 1-844-817-6468, Option 2.
Let's Talk. We're available Monday-Friday, 8AM-8PM ET.

Please see accompanying EXKIVITY™ full Prescribing Information, including Boxed Warning.
Please see accompanying ICLUSIG® full Prescribing Information, including Boxed Warning.

Takeda | ONCOLOGY

ICLUSIG® (ponatinib) tablets 45mg / 30mg / 15mg / 10mg

Access Guide

INDICATIONS AND USAGE

ICLUSIG® (ponatinib) is a kinase inhibitor indicated for the treatment of adult patients with:

- Chronic phase (CP) chronic myeloid leukemia (CML) with resistance or intolerance to at least two prior kinase inhibitors.
- Accelerated phase (AP) or blast phase (BP) CML or Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) for whom no other kinase inhibitors are indicated.
- T315I-positive CML (chronic phase, accelerated phase, or blast phase) or T315I-positive Ph+ ALL.

Limitations of Use: ICLUSIG is not indicated and is not recommended for the treatment of patients with newly diagnosed CP-CML.

IMPORTANT SAFETY INFORMATION

WARNING: ARTERIAL OCCLUSIVE EVENTS, VENOUS THROMBOEMBOLIC EVENTS, HEART FAILURE, and HEPATOTOXICITY

See full prescribing information for complete boxed warning.

- **Arterial occlusive events (AOEs), including fatalities, have occurred in ICLUSIG-treated patients. AOEs included fatal myocardial infarction, stroke, stenosis of large arterial vessels of the brain, severe peripheral vascular disease, and the need for urgent revascularization procedures. Patients with and without cardiovascular risk factors, including patients age 50 years or younger, experienced these events. Monitor for evidence of AOEs. Interrupt or discontinue ICLUSIG based on severity. Consider benefit-risk to guide a decision to restart ICLUSIG.**
- **Venous thromboembolic events (VTEs) have occurred in ICLUSIG-treated patients. Monitor for evidence of VTEs. Interrupt or discontinue ICLUSIG based on severity.**
- **Heart failure, including fatalities, occurred in ICLUSIG-treated patients. Monitor for heart failure and manage patients as clinically indicated. Interrupt or discontinue ICLUSIG for new or worsening heart failure.**
- **Hepatotoxicity, liver failure and death have occurred in ICLUSIG-treated patients. Monitor liver function tests. Interrupt or discontinue ICLUSIG based on severity.**

Please see Important Safety Information on pages 4-6 and accompanying full Prescribing Information, including Boxed Warning.

Takeda Oncology Here2Assist

Please see page 3 to learn more.

Takeda | ONCOLOGY

Distribution Details for ICLUSIG® (ponatinib)

Product name	ICLUSIG® (ponatinib) tablets, for oral use
Distributed and marketed by	Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited
Storage and handling	Store ICLUSIG tablets at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].
Recommended dosing	**Patients with CP-CML:** The recommended starting dose is 45 mg orally once daily with a reduction to 15 mg once daily upon achievement of ≤1% BCR-ABL1[IS]. Patients with loss of response can re-escalate the dose of ICLUSIG to a previously tolerated dose of 30 mg or 45 mg once daily. Continue ICLUSIG until loss of response at the re-escalated dose or unacceptable toxicity. Consider discontinuing ICLUSIG if hematologic response has not occurred by 3 months. **Patients with AP-CML, BP-CML, and Ph+ ALL:** The optimal dose of ICLUSIG has not been identified. The recommended starting dose is 45 mg orally once daily. Consider reducing the dose of ICLUSIG for patients with AP-CML who have achieved a major cytogenetic response. Continue ICLUSIG until loss of response or unacceptable toxicity. Consider discontinuing ICLUSIG if response has not occurred by 3 months.

How supplied

Strength	Count	NDC Number
45 mg	Bottle of 30 tablets	63020-534-30
30 mg	Bottle of 30 tablets	63020-533-30
15 mg	Bottle of 30 tablets	63020-535-30
10 mg	Bottle of 30 tablets	63020-536-30

ICLUSIG tablets are supplied in wide-mouth white high-density polyethylene (HDPE) bottles with a desiccant canister and induction-sealed, child-resistant closure

Ordering

ICLUSIG is available through an exclusive, integrated specialty pharmacy:

AcariaHealth
833-442-8911
www.acariahealth.com

There are 2 ways to order ICLUSIG via the AcariaHealth Specialty Pharmacy:

1. Submit the ICLUSIG prescription to any AcariaHealth in your e-prescribing system.
2. Complete the ICLUSIG Referral Form provided by AcariaHealth at acariahealth.envolvehealth.com/resources/referral-forms1.html and fax to AcariaHealth as directed on the form.

ICLUSIG must be filled through AcariaHealth. Sending an ICLUSIG prescription to an alternate pharmacy may result in delay or nonfulfillment of the prescription.

ICLUSIG may be purchased directly by qualified entities* from our exclusive distribution partner:

AcariaHealth
ICLUSIGDirect Purchase Program
833-291-2773
www.ICLUSIGDirect.com

NDC, National Drug Code; USP, United States Pharmacopeia.

*Qualified entities for direct purchase include hospitals, physician practices, and institutions that have been licensed by a state agency to dispense pharmaceutical products to appropriate patients, excluding specialty pharmacy providers and retail pharmacies. Eligible government entities include the Department of Defense, Department of Veterans Affairs, and 340B covered entities.

Please see Important Safety Information on pages 4-6 and accompanying full Prescribing Information, including Boxed Warning.

ICLUSIG® (ponatinib) tablets
45mg / 30mg / 15mg / 10mg

Takeda Oncology Here2Assist

We're here to help with coverage, financial, and educational resource needs

Takeda Oncology Here2Assist™:

- **Works with** your patients' insurance companies to conduct benefits verifications and provides coverage options to your office
- **Identifies** available financial assistance that may be right for your patients
- **May help** eligible patients get started on treatment in the event of an insurance delay
- **Can identify** a specialty pharmacy to help fill and ship your patients' prescriptions appropriately

For more information about access support and financial assistance that your patients may qualify for, call us at 1-844-817-6468, Option 2. Let's Talk. We're available Monday-Friday, 8AM–8PM ET, or visit us at www.Here2Assist.com to learn more.

The Takeda Oncology Here2Assist RapidStart Program

If your patient experiences a delay in insurance coverage determination of at least 5 business days, your patient may be eligible to receive a 1-month supply of medication at no cost to them. Terms and Conditions apply.*

Visit www.Here2Assist.com to download the appropriate RapidStart Request Form.

Takeda Oncology Co-Pay Assistance Program

For patients who are commercially insured and concerned about their out-of-pocket costs, the Takeda Oncology Co-Pay Assistance Program† may be able to help.

Your patient could pay as little as $10 per prescription. Terms and Conditions apply.†

Visit www.TakedaOncologyCopay.com or call to speak with a Takeda Oncology Here2Assist case manager at 1-844-817-6468, Option 2, Monday-Friday, 8AM–8PM ET.

Takeda Oncology Patient Assistance Program

If your patient is uninsured or the prescribed medication is not covered, the patient may be eligible to receive medication at no cost through our Patient Assistance Program.‡

Visit www.Here2Assist.com to download the Patient Assistance Program Application.

*The RapidStart Program provides a 1-month supply of treatment of the prescribed Takeda Oncology medication at no charge for eligible patients new to therapy experiencing a delay in insurance coverage determination of at least 5 business days. There is no purchase obligation by virtue of a patient's participation in the RapidStart Program. Patients must have an on-label, valid prescription for the Takeda Oncology medication, and a medical necessity for being prescribed the Takeda Oncology medication. Patients must be enrolled in the Takeda Oncology Here2Assist Program to qualify. Free product for the RapidStart Program will only be available through the RapidStart Program noncommercial specialty pharmacy. A delay in coverage determination of at least 5 days is required for patients to be eligible for the RapidStart Program. The program may not be combined with any other offer and is not available to patients whose insurers have made a final determination to deny the patient coverage for the prescribed Takeda Oncology medication. Takeda reserves the right to change or end the program at any time. Benefits provided under the program are not transferable.

†Takeda Oncology Co-Pay Assistance Program Terms and Conditions: This offer cannot be used if you are a beneficiary of, or any part of your prescription is covered or reimbursed by: (1) any federal or state healthcare program (Medicare, Medicaid, TRICARE, Veterans Administration, Department of Defense, etc.), including a state or territory pharmaceutical assistance program, (2) the Medicare Prescription Drug Program (Part D), or if you are currently in the coverage gap, Medicare Advantage Plans, Medicaid Managed Care or Alternative Benefit Plans under the Affordable Care Act, or Medigap, or (3) insurance that is paying the entire cost of the prescription. Patients must be at least 18 years old.
You must meet Eligibility Requirements. You agree to report your use of this offer to any third party that reimburses you or pays for any part of the prescription price. Use of this offer is confirmation that you are permitted, under the terms and conditions of the health benefit plan(s) covering your prescription, to take advantage of co-pay assistance programs. You additionally agree that you will not submit the cost of any portion of the product dispensed pursuant to this offer to a federal or state healthcare program (Medicare, Medicaid, TRICARE, Veterans Administration, Department of Defense, etc.), for purposes of counting it toward your out-of-pocket expenses, and to notify Takeda Oncology Here2Assist™ if you become eligible for a federal or state healthcare program. This assistance program covers out-of-pocket expenses greater than $10 per monthly prescription. Maximum $25,000 annually. Your co-pay card can be renewed every 12 months, subject to continued eligibility. This offer is not valid with any other program, discount, or offer involving your prescribed Takeda Oncology medication. This offer may be rescinded, revoked, or amended without notice. No reproductions. This offer is void where prohibited by law, taxed, or restricted. Limit one offer per purchase. Cash value of 1/100 of 1¢. For questions about this offer, please contact the Takeda Oncology Co-Pay Assistance Program, a patient support service of Takeda Oncology Here2Assist, at 1-844-817-6468, Option 2, Monday-Friday, 8AM-8PM ET.

‡To be eligible for the Patient Assistance Program, patients must meet certain financial and insurance coverage criteria. A Patient Assistance Program Application must be submitted in order to confirm patient eligibility.

IMPORTANT SAFETY INFORMATION (CONT'D)

WARNINGS AND PRECAUTIONS

Arterial Occlusive Events (AOEs): AOEs, including fatalities, have occurred in patients who received ICLUSIG in OPTIC and PACE. These included cardiovascular, cerebrovascular, and peripheral vascular events. The incidence of AOEs in OPTIC (45 mg →15 mg) was 13% of 94 patients; 5% experienced Grade 3 or 4. In PACE, the incidence of AOEs was 26% of 449 patients; 14% experienced Grade 3 or 4. Fatal AOEs occurred in 2.1% of patients in OPTIC, and in 2% of patients in PACE. Some patients in PACE experienced recurrent or multisite vascular occlusion. Patients with and without cardiovascular risk factors, including patients age 50 years or younger, experienced these events. The most common risk factors observed with these events in PACE were history of hypertension, hypercholesterolemia, and non-ischemic cardiac disease. In OPTIC and PACE, AOEs were more frequent with increasing age.

In OPTIC, patients with uncontrolled hypertension or diabetes and patients with clinically significant, uncontrolled, or active cardiovascular disease were excluded. In PACE, patients with uncontrolled hypertriglyceridemia and patients with clinically significant or active cardiovascular disease within the 3 months prior to the first dose of ICLUSIG were excluded. Consider whether the benefits of ICLUSIG are expected to exceed the risks.

Monitor for evidence of AOEs. Interrupt, then resume at the same or decreased dose or discontinue ICLUSIG based on recurrence/severity. Consider benefit-risk to guide a decision to restart ICLUSIG.

Venous Thromboembolic Events (VTEs): Serious or severe VTEs have occurred in patients who received ICLUSIG. In PACE, VTEs occurred in 6% of 449 patients including serious or severe (Grade 3 or 4) VTEs in 5.8% of patients. VTEs included deep venous thrombosis, pulmonary embolism, superficial thrombophlebitis, retinal vein occlusion, and retinal vein thrombosis with vision loss. The incidence was higher in patients with Ph+ ALL (9% of 32 patients) and BP-CML (10% of 62 patients). One of 94 patients in OPTIC experienced a VTE (Grade 1 retinal vein occlusion). Monitor for evidence of VTEs. Interrupt, then resume at the same or decreased dose or discontinue ICLUSIG based on recurrence/severity.

Heart Failure: Fatal, serious or severe heart failure events have occurred in patients who received ICLUSIG. In PACE, heart failure occurred in 9% of 449 patients; 7% experienced serious or severe (Grade 3 or higher). Heart failure occurred in 12% of 94 patients in OPTIC; 1.1% experienced serious or severe (Grade 3 or 4). In PACE, the most frequently reported heart failure events (≥2%) were congestive cardiac failure (3.1%), decreased ejection fraction (2.9%), and cardiac failure (2%). In OPTIC, the most frequently reported heart failure events (>1 patient each) were left ventricular hypertrophy (2.1%) and BNP increased (2.1%). Monitor patients for signs or symptoms consistent with heart failure and manage heart failure as clinically indicated. Interrupt, then resume at reduced dose or discontinue ICLUSIG for new or worsening heart failure.

Hepatotoxicity: ICLUSIG can cause hepatotoxicity, including liver failure and death. Fulminant hepatic failure leading to death occurred in 3 patients, with hepatic failure occurring within 1 week of starting ICLUSIG in one of these patients. These fatal cases occurred in patients with BP-CML or Ph+ ALL. Hepatotoxicity occurred in 25% of 94 patients in OPTIC and 32% of 449 patients in PACE. Grade 3 or 4 hepatotoxicity occurred in OPTIC (6% of 94 patients) and PACE (13% of 449 patients). The most frequent hepatotoxic events were elevations of ALT, AST, GGT, bilirubin, and alkaline phosphatase. Monitor liver function tests at baseline, then at least monthly or as clinically indicated. Interrupt, then resume at a reduced dose or discontinue ICLUSIG based on recurrence/severity.

Hypertension: Serious or severe hypertension, including hypertensive crisis, has occurred in patients who received ICLUSIG. Patients may require urgent clinical intervention for hypertension associated with confusion, headache, chest pain, or shortness of breath. Monitor blood pressure at baseline and as clinically indicated and manage hypertension as clinically indicated. Interrupt, dose reduce, or stop ICLUSIG if hypertension is not medically controlled. For significant worsening, labile or treatment-resistant hypertension, interrupt ICLUSIG and consider evaluating for renal artery stenosis.

IMPORTANT SAFETY INFORMATION (CONT'D)

WARNINGS AND PRECAUTIONS (CONT'D)

Pancreatitis: Serious or severe pancreatitis has occurred in patients who received ICLUSIG. Elevations of lipase and amylase also occurred. In the majority of cases that led to dose modification or treatment discontinuation, pancreatitis resolved within 2 weeks. Monitor serum lipase every 2 weeks for the first 2 months and then monthly thereafter or as clinically indicated. Consider additional serum lipase monitoring in patients with a history of pancreatitis or alcohol abuse. Interrupt, then resume at the same or reduced dose or discontinue ICLUSIG based on severity. Evaluate for pancreatitis when lipase elevation is accompanied by abdominal symptoms.

Increased Toxicity in Newly Diagnosed Chronic Phase CML: In a prospective randomized clinical trial in the first line treatment of newly diagnosed patients with CP-CML, single agent ICLUSIG 45 mg once daily increased the risk of serious adverse reactions 2-fold compared to single agent imatinib 400 mg once daily. The median exposure to treatment was less than 6 months. The trial was halted for safety. Arterial and venous thrombosis and occlusions occurred at least twice as frequently in the ICLUSIG arm compared to the imatinib arm. Compared to imatinib-treated patients, ICLUSIG-treated patients exhibited a greater incidence of myelosuppression, pancreatitis, hepatotoxicity, cardiac failure, hypertension, and skin and subcutaneous tissue disorders. ICLUSIG is not indicated and is not recommended for the treatment of patients with newly diagnosed CP-CML.

Neuropathy: Peripheral and cranial neuropathy occurred in patients in OPTIC and PACE. Some of these events in PACE were Grade 3 or 4. Monitor patients for symptoms of neuropathy, such as hypoesthesia, hyperesthesia, paresthesia, discomfort, a burning sensation, neuropathic pain or weakness. Interrupt, then resume at the same or reduced dose or discontinue ICLUSIG based on recurrence/severity.

Ocular Toxicity: Serious or severe ocular toxicity leading to blindness or blurred vision have occurred in ICLUSIG-treated patients. The most frequent ocular toxicities occurring in OPTIC and PACE were dry eye, blurred vision, and eye pain. Retinal toxicities included age-related macular degeneration, macular edema, retinal vein occlusion, retinal hemorrhage, and vitreous floaters. Conduct comprehensive eye exams at baseline and periodically during treatment.

Hemorrhage: Fatal and serious hemorrhage events have occurred in patients who received ICLUSIG. Fatal hemorrhages occurred in PACE and serious hemorrhages occurred in OPTIC and PACE. The incidence of serious bleeding events was higher in patients with AP-CML, BP-CML, and Ph+ ALL. Gastrointestinal hemorrhage and subdural hematoma were the most frequently reported serious hemorrhages. Events often occurred in patients with Grade 4 thrombocytopenia. Monitor for hemorrhage and manage patients as clinically indicated. Interrupt, then resume at the same or reduced dose or discontinue ICLUSIG based on recurrence/severity.

Fluid Retention: Fatal and serious fluid retention events have occurred in patients who received ICLUSIG. In PACE, one instance of brain edema was fatal and serious events included pleural effusion, pericardial effusion, and angioedema. Monitor for fluid retention and manage patients as clinically indicated. Interrupt, then resume at the same or reduced dose or discontinue ICLUSIG based on recurrence/severity.

Cardiac Arrhythmias: Cardiac arrhythmias, including ventricular and atrial arrhythmias, occurred in patients in OPTIC and PACE. For some patients, events were serious or severe (Grade 3 or 4) and led to hospitalization. Monitor for signs and symptoms suggestive of slow heart rate (fainting, dizziness) or rapid heart rate (chest pain, palpitations or dizziness) and manage patients as clinically indicated. Interrupt, then resume at the same or reduced dose or discontinue ICLUSIG based on recurrence/severity.

Myelosuppression: Grade 3 or 4 events of neutropenia, thrombocytopenia, and anemia occurred in patients in OPTIC and PACE. The incidence of myelosuppression was greater in patients with AP-CML, BP-CML, and Ph+ ALL than in patients with CP-CML. Obtain complete blood counts every 2 weeks for the first 3 months and then monthly or as clinically indicated. If ANC less than 1×10^9/L or platelets less than 50×10^9/L, interrupt ICLUSIG until ANC at least 1.5×10^9/L and platelets at least 75×10^9/L, then resume at same or reduced dose.

Tumor Lysis Syndrome (TLS): Serious TLS was reported in ICLUSIG-treated patients in OPTIC and PACE. Ensure adequate hydration and treat high uric acid levels prior to initiating ICLUSIG.

IMPORTANT SAFETY INFORMATION (CONT'D)

WARNINGS AND PRECAUTIONS (CONT'D)

Reversible Posterior Leukoencephalopathy Syndrome (RPLS): RPLS (also known as Posterior Reversible Encephalopathy Syndrome) has been reported in patients who received ICLUSIG. Along with neurological signs and symptoms, hypertension may be present. Diagnosis is made with supportive findings on magnetic resonance imaging (MRI) of the brain. Interrupt ICLUSIG until resolution. The safety of resumption of ICLUSIG in patients upon resolution of RPLS is unknown.

Impaired Wound Healing and Gastrointestinal Perforation: Impaired wound healing occurred in patients receiving ICLUSIG. Withhold ICLUSIG for at least 1 week prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of ICLUSIG after resolution of wound healing complications has not been established. Gastrointestinal perforation or fistula occurred in patients receiving ICLUSIG. Permanently discontinue in patients with gastrointestinal perforation.

Embryo-Fetal Toxicity: Based on its mechanism of action and findings from animal studies, ICLUSIG can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, adverse developmental effects occurred at exposures lower than human exposures at the recommended human dose. Advise pregnant women of the potential risk to the fetus. Advise females of reproductive potential to use effective contraception during treatment with ICLUSIG and for 3 weeks after the last dose.

ADVERSE REACTIONS

The most common (>20%) adverse reactions are rash and related conditions, arthralgia, abdominal pain, headache, constipation, dry skin, hypertension, fatigue, fluid retention and edema, pyrexia, nausea, pancreatitis/lipase elevation, hemorrhage, anemia, hepatic dysfunction and AOEs. The most common Grade 3 or 4 laboratory abnormalities (>20%) are platelet count decreased, neutrophil cell count decreased, and white blood cell decreased.

To report SUSPECTED ADVERSE REACTIONS, contact Takeda Pharmaceutical Co. Ltd. at 1-844-817-6468 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Strong CYP3A Inhibitors: Avoid coadministration or reduce ICLUSIG dose if coadministration cannot be avoided.

Strong CYP3A Inducers: Avoid coadministration.

USE IN SPECIFIC POPULATIONS

Females and Males of Reproductive Potential: Verify pregnancy status of females of reproductive potential prior to initiating ICLUSIG.
Ponatinib may impair fertility in females, and it is not known if these effects are reversible.

Lactation: Advise women not to breastfeed during treatment with ICLUSIG and for 6 days following last dose.

Please see accompanying full Prescribing Information, including Boxed Warning.

To learn more about ICLUSIG, please visit www.iclusig.com/hcp.

Notes

Takeda | ONCOLOGY

ICLUSIG®
(ponatinib) tablets
45mg / 30mg / 15mg / 10mg


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