ROMIDEPSIN- romidepsin injection, solution, concentrate
Amneal Pharmaceuticals LLC

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

ROMIDEPSIN injection, for intravenous use
Initial U.S. Approval: 2009

INDICATIONS AND USAGE

Romidepsin injection is a histone deacetylase (HDAC) inhibitor indicated for the treatment of cutaneous T-cell lymphoma (CTCL) in adult patients who have received at least one prior systemic therapy. (1)

DOSAGE AND ADMINISTRATION

- 14 mg/m^2 administered intravenously over a 4-hour period on days 1, 8, and 15 of a 28-day cycle. Repeat cycles every 28 days provided that the patient continues to benefit from and tolerates the drug. (2.1)
- Discontinue or interrupt treatment (with or without dose reduction to 10 mg/m^2) to manage drug toxicity. (2.2)
- Reduce starting dose in patients with moderate and severe hepatic impairment. (2.3)

DOSAGE FORMS AND STRENGTHS

Injection: 27.5 mg/5.5 mL (5 mg/mL) in single-dose vial. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Myelosuppression: Romidepsin can cause thrombocytopenia, leukopenia (neutropenia and lymphopenia), and anemia; monitor blood counts during treatment with romidepsin injection; interrupt and/or modify the dose as necessary. (5.1)
- Infections: Fatal and serious infections. Reactivation of DNA viruses (Epstein Barr and hepatitis B). Consider monitoring and prophylaxis in patients with evidence of prior hepatitis B. (5.2)
- Electrocardiographic (ECG) changes: Consider cardiovascular monitoring in patients with congenital long QT syndrome, a history of significant cardiovascular disease, and patients taking medicinal products that lead to significant QT prolongation. Ensure that potassium and magnesium are within the normal range before administration of romidepsin injection. (5.3)
- Tumor lysis syndrome: Patients with advanced stage disease and/or high tumor burden are at greater risk and should be closely monitored and appropriate precautions taken. (5.4)
- Embryo-fetal toxicity: Can cause fetal harm. Advise females of reproductive potential and males with female partners of reproductive potential of potential risk to a fetus and to use effective contraception. (5.5, 8.1, 8.3)

ADVERSE REACTIONS

The most common adverse reactions (≥ 30%), excluding laboratory abnormalities, are nausea, fatigue, infections, vomiting, anorexia, electrocardiogram ST-T wave changes, dysgeusia, constipation and pruritus. Grade 3 to 4 laboratory abnormalities (≥ 10%) include lymphopenia, neutropenia, anemia and thrombocytopenia. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Amneal Pharmaceuticals LLC at 1-877-835-5472 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Warfarin: Carefully monitor prothrombin time (PT) and International Normalized Ratio (INR) in patients receiving concurrent warfarin or coumarin derivatives. (7.1)
- CYP3A4 inhibitors: Monitor for toxicities related to increased romidepsin exposure when co-administering romidepsin with strong CYP3A4 inhibitors. (7.2)
- CYP3A4 inducers: Avoid use with rifampin and strong CYP3A4 inducers. (7.3)

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

Revised: 9/2025

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Romidepsin injection is indicated for the treatment of cutaneous T-cell lymphoma (CTCL) in adult patients who have received at least one prior systemic therapy.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage Information

The recommended dosage of romidepsin injection is 14 mg/m^2 administered intravenously over a 4-hour period on days 1, 8, and 15 of a 28-day cycle. Cycles should be repeated every 28 days provided that the patient continues to benefit from and tolerates the drug.

2.2 Dosage Modification

Nonhematologic toxicities except alopecia

- Grade 2 or 3 toxicity: Treatment with romidepsin injection should be delayed until toxicity returns to Grade 0 to 1 or baseline, then therapy may be restarted at 14 mg/m^2. If Grade 3 toxicity recurs, treatment with romidepsin injection should be delayed until toxicity returns to Grade 0 to 1 or baseline and the dose should be permanently reduced to 10 mg/m^2.
- Grade 4 toxicity: Treatment with romidepsin injection should be delayed until toxicity returns to Grade 0 to 1 or baseline, then the dose should be permanently reduced to 10 mg/m^2.
- Romidepsin injection should be discontinued if Grade 3 or 4 toxicities recur after dose reduction.

Hematologic toxicities

- Grade 3 or 4 neutropenia or thrombocytopenia: Treatment with romidepsin injection should be delayed until the specific cytopenia returns to ANC greater than or equal to 1.5 × 10^9/L and platelet count greater than or equal to 75 × 10^9/L or baseline, then therapy may be restarted at 14 mg/m^2.
- Grade 4 febrile (greater than or equal to 38.5°C) neutropenia or thrombocytopenia that requires platelet transfusion: Treatment with romidepsin injection should be delayed until the specific cytopenia returns to less than or equal to Grade 1 or baseline, and then the dose should be permanently reduced to 10 mg/m^2.

2.3 Dosage in Patients with Hepatic Impairment

For patients with moderate or severe hepatic impairment, reduce the starting dose of romidepsin injection as shown in Table 1 and monitor for toxicities more frequently. Dosage adjustment is not required for patients with mild hepatic impairment.

Table 1: Recommendations for Starting Dose in Patients with Moderate and Severe Hepatic Impairment

Hepatic Impairment	Bilirubin Levels	Romidepsin Injection Dose

Moderate	greater than 1.5 × ULN to less than or equal to 3 × ULN	7 mg/m^2
Severe	greater than 3 × ULN	5 mg/m^2
ULN = Upper limit of normal.		

2.4 Instructions for Preparation and Intravenous Administration

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

Romidepsin injection must be diluted with 0.9% Sodium Chloride Injection, USP before intravenous infusion.

- Extract the appropriate amount of romidepsin injection from the vial to deliver the desired dose, using proper aseptic technique. Before intravenous infusion, dilute romidepsin injection in 500 mL 0.9% Sodium Chloride Injection, USP.
- Infuse over 4 hours.
- Discard unused portion.

The diluted solution is compatible with polyvinyl chloride (PVC), ethylene vinyl acetate (EVA), polyethylene (PE) infusion bags as well as glass bottles, and is chemically stable for up to 24 hours when stored at room temperature. However, it should be administered as soon after dilution as possible.

Parenteral drug products should be inspected visually for particulate matter and discoloration before administration, whenever solution and container permit.

3 DOSAGE FORMS AND STRENGTHS

Injection: 27.5 mg/5.5 mL (5 mg/mL) in single-dose vial.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Myelosuppression

Treatment with romidepsin can cause thrombocytopenia, leukopenia (neutropenia and lymphopenia), and anemia. Monitor blood counts regularly during treatment with romidepsin injection and modify the dose as necessary *[see Dosage and Administration (2.2)* and *Adverse Reactions (6.1)]*.

5.2 Infections

Fatal and serious infections have been reported in clinical trials of romidepsin, including pneumonia, sepsis, and viral reactivation, including reactivation of Epstein Barr and hepatitis B viruses. These infections can occur during and following treatment. The risk

of life-threatening infections may be greater in patients with a history of prior treatment with monoclonal antibodies directed against lymphocyte antigens and in patients with disease involvement of the bone marrow *[see Adverse Reactions (6.1)]*.

Reactivation of hepatitis B virus infection was reported in 1% of patients in clinical trials. In patients with evidence of prior hepatitis B infection, consider monitoring for reactivation, and consider antiviral prophylaxis.

Reactivation of Epstein Barr viral infection leading to liver failure has occurred in recipients of romidepsin including after ganciclovir prophylaxis.

5.3 Electrocardiographic Changes

Several treatment-emergent morphological changes in ECGs (including T-wave and ST-segment changes) have been reported in clinical studies. The clinical significance of these changes is unknown *[see Adverse Reactions (6.1)]*.

In patients with congenital long QT syndrome, patients with a history of significant cardiovascular disease, and patients taking anti-arrhythmic medicines or medicinal products that lead to significant QT prolongation, consider cardiovascular monitoring of ECGs at baseline and periodically during treatment.

Confirm that potassium and magnesium levels are within normal range before administration of romidepsin injection *[see Adverse Reactions (6.1)]*.

5.4 Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) has been reported to occur in recipients of romidepsin, including in 1% of patients with tumor stage CTCL. Patients with advanced stage disease and/or high tumor burden are at greater risk, should be closely monitored, and managed as appropriate.

5.5 Embryo-Fetal Toxicity

Based on its mechanism of action and findings from animal studies, romidepsin injection can cause fetal harm when administered to a pregnant woman. In an animal reproductive study, romidepsin was embryocidal and caused adverse developmental outcomes at exposures below those in patients at the recommended dose of 14 mg/m^2. Advise females of reproductive potential to use effective contraception during treatment and for 1 month after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment and for 1 month after the last dose *[see Use in Specific Populations (8.1, 8.3)* and *Clinical Pharmacology (12.1)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described in more detail in other sections of the prescribing information.

- Myelosuppression *[see Warnings and Precautions (5.1)]*
- Infections *[see Warnings and Precautions (5.2)]*
- Electrocardiographic Changes *[see Warnings and Precautions (5.3)]*
- Tumor Lysis Syndrome *[see Warnings and Precautions (5.4)]*

6.1 Clinical Trials Experience

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

The data in the WARNINGS AND PRECAUTIONS reflect exposure to romidepsin in four clinical trials involving 363 patients with T-cell lymphoma, including 185 patients with CTCL. Romidepsin was administered as a single agent at a dosage of 14 mg/m^2 on days 1, 8, and 15 of a 28-day cycle. Among 363 patients who received romidepsin, 21% were exposed for 6 months or longer and 13% were exposed for greater than one year.

Cutaneous T-Cell Lymphoma

The safety of romidepsin was evaluated in 185 patients with CTCL in 2 single arm clinical studies in which patients received a dosage of 14 mg/m^2 on days 1, 8, and 15 of a 28-day cycle. Treatment continued as long as the patient benefitted from and tolerated the drug. The mean duration of treatment in these studies was 5.6 months (range: < 1 month to 83.4 months).

Common Adverse Reactions

Table 2 summarizes the most frequent adverse reactions (> 20%) regardless of causality using the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE, Version 3.0). Due to methodological differences between the studies, the AE data are presented separately for Study 1 and Study 2. Adverse reactions are ranked by their incidence in Study 1. Laboratory abnormalities commonly reported (> 20%) as adverse reactions are included in Table 2.

Table 2: Adverse Reactions Occurring in > 20% of Patients in Either CTCL Study (N=185)

Adverse Reactions n (%)	**Study 1 (n = 102)**		**Study 2 (n = 83)**	
	All grades	**Grade 3 or 4**	**All grades**	**Grade 3 or 4**
Any adverse reactions	*99 (97)*	*36 (35)*	*83 (100)*	*68 (82)*
Nausea	57 (56)	3 (3)	71 (86)	5 (6)
Asthenia/Fatigue	54 (53)	8 (8)	64 (77)	12 (14)
Infections	47 (46)	11 (11)	45 (54)	27 (33)
Vomiting	35 (34)	1 (< 1)	43 (52)	8 (10)
Anorexia	23 (23)	1 (< 1)	45 (54)	3 (4)
Hypomagnesemia	22 (22)	1 (< 1)	23 (28)	0
Diarrhea	20 (20)	1 (< 1)	22 (27)	1 (1)
Pyrexia	20 (20)	4 (4)	19 (23)	1 (1)
Anemia	19 (19)	3 (3)	60 (72)	13 (16)
Thrombocytopenia	17 (17)	0	54 (65)	12 (14)
Dysgeusia	15 (15)	0	33 (40)	0

Constipation	12 (12)	2 (2)	32 (39)	1 (1)
Neutropenia	11 (11)	4 (4)	47 (57)	22 (27)
Hypotension	7 (7)	3 (3)	19 (23)	3 (4)
Pruritus	7 (7)	0	26 (31)	5 (6)
Hypokalemia	6 (6)	0	17 (20)	2 (2)
Dermatitis/Exfoliative dermatitis	4 (4)	1 (< 1)	22 (27)	7 (8)
Hypocalcemia	4 (4)	0	43 (52)	5 (6)
Leukopenia	4 (4)	0	38 (46)	18 (22)
Lymphopenia	4 (4)	0	47 (57)	31 (37)
Alanine aminotransferase increased	3 (3)	0	18 (22)	2 (2)
Aspartate aminotransferase increased	3 (3)	0	23 (28)	3 (4)
Hypoalbuminemia	3 (3)	1 (< 1)	40 (48)	3 (4)
Electrocardiogram ST-T wave changes	2 (2)	0	52 (63)	0
Hyperglycemia	2 (2)	2 (2)	42 (51)	1 (1)
Hyponatremia	1 (< 1)	1 (< 1)	17 (20)	2 (2)
Hypermagnesemia	0	0	22 (27)	7 (8)
Hypophosphatemia	0	0	22 (27)	8 (10)
Hyperuricemia	0	0	27 (33)	7 (8)

Serious Adverse Reactions

Infections were the most common type of SAE reported in both studies with 8 patients (8%) in Study 1 and 26 patients (31%) in Study 2 experiencing a serious infection. Serious adverse reactions reported in > 2% of patients in Study 1 were sepsis and pyrexia (3%). In Study 2, serious adverse reactions in > 2% of patients were fatigue (7%), supraventricular arrhythmia, central line infection, neutropenia (6%), hypotension, hyperuricemia, edema (5%), ventricular arrhythmia, thrombocytopenia, nausea, leukopenia, dehydration, pyrexia, aspartate aminotransferase increased, sepsis, catheter related infection, hypophosphatemia and dyspnea (4%).

There were eight deaths not due to disease progression. In Study 1, there were two deaths: one due to cardiopulmonary failure and one due to acute renal failure. There were six deaths in Study 2: four due to infection and one each due to myocardial ischemia and acute respiratory distress syndrome.

Discontinuations

Discontinuation due to an adverse event occurred in 21% of patients in Study 1 and 11% in Study 2. Discontinuations occurring in at least 2% of patients in either study included infection, fatigue, dyspnea, QT prolongation, and hypomagnesemia.

Other Clinical Trials Experience

The following common adverse reactions have been reported following administration of romidepsin as a single agent in 178 patients with peripheral T-cell lymphoma, for which

romidepsin is not indicated or recommended. The most common adverse reactions (≥ 30%) included nausea (63%), fatigue (61%), thrombocytopenia (49%), vomiting (39%), neutropenia (39%), pyrexia (38%), diarrhea (36%) and anemia (35%). Other common (≥ 10%) clinically significant adverse reactions included dysgeusia (22%), headache (20%), cough (19%), dyspnea (15%), abdominal pain (13%) and stomatitis (10%). Grade 3 and higher adverse reactions in ≥ 10% were hematologic toxicities (including thrombocytopenia, neutropenia, leukopenia and anemia) and fatigue.

7 DRUG INTERACTIONS

7.1 Warfarin or Coumarin Derivatives

Prolongation of PT and elevation of INR were observed in a patient receiving romidepsin concomitantly with warfarin. Monitor PT and INR more frequently in patients concurrently receiving romidepsin injection and warfarin *[see Clinical Pharmacology (12.3)]*.

7.2 Drugs That Inhibit CYP3A4 Enzymes

Strong CYP3A4 inhibitors increase concentrations of romidepsin *[see Clinical Pharmacology (12.3)]*. Monitor for toxicity related to increased romidepsin exposure and follow the dose modifications for toxicity *[see Dosage and Administration (2.2)]* when romidepsin injection is initially co-administered with strong CYP3A4 inhibitors.

7.3 Drugs That Induce CYP3A4 Enzymes

Rifampin (a potent CYP3A4 inducer) increased the concentrations of romidepsin *[see Clinical Pharmacology (12.3)]*. Avoid co-administration of romidepsin injection with rifampin. The use of other potent CYP3A4 inducers should be avoided when possible.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action and findings from animal studies, romidepsin injection can cause embryo-fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1)]*. There are no available data on romidepsin use in pregnant women to inform a drug associated risk of major birth defects and miscarriage. In an animal reproductive study, romidepsin was embryocidal and caused adverse developmental outcomes including embryo-fetal toxicity and malformations at exposures below those in patients at the recommended dose *(see Data)*. Advise pregnant women of the potential risk to a fetus and to avoid becoming pregnant while receiving romidepsin and for at least 1 month after the last dose.

The 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

Animal Data

Romidepsin was administered intravenously to pregnant rats during the period of organogenesis at doses of 0.1, 0.2, or 0.5 mg/kg/day. Substantial resorption or postimplantation loss was observed at the high dose of 0.5 mg/kg/day, a maternally toxic dose. Adverse embryo-fetal effects were noted at romidepsin doses of ≥ 0.1 mg/kg/day, with systemic exposures (AUC) ≥ 0.2% of the human exposure at the recommended dose of 14 mg/m^2/week. Drug-related fetal effects consisted of reduced fetal body weights, folded retina, rotated limbs, and incomplete sternal ossification.

8.2 Lactation

Risk Summary

There are no data on the presence of romidepsin or its metabolites in human milk, the effects on the breastfed child, or the effects on milk production. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in the breastfed child, advise lactating women not to breastfeed during treatment with romidepsin injection and for 1 week after the last dose.

8.3 Females and Males of Reproductive Potential

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

Pregnancy Testing

Perform pregnancy testing in females of reproductive potential within 7 days prior to initiating therapy with romidepsin injection.

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment with romidepsin injection and for 1 month after the last dose. Romidepsin may reduce the effectiveness of estrogen-containing contraceptives. Therefore, alternative methods of non-estrogen containing contraception (e.g., condoms, intrauterine devices) should be used in patients receiving romidepsin injection.

Males

Advise males with female partners of reproductive potential to use effective contraception during treatment with romidepsin injection and for 1 month after the last dose.

Infertility

Based on findings in animals, romidepsin has the potential to affect male and female fertility *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

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

8.5 Geriatric Use

Of the 186 patients with CTCL who received romidepsin in clinical studies, 51 (28%) were 65 years of age and older, while 16 (9%) were 75 years of age. No overall differences in safety or effectiveness were observed between patients 65 years or age and over and younger patients; however, greater sensitivity of some older individuals cannot be ruled out.

8.6 Hepatic Impairment

In a hepatic impairment study, romidepsin was evaluated in 19 patients with advanced cancer and mild (8), moderate (5), or severe (6) hepatic impairment. There were 4 deaths during the first cycle of treatment: 1 patient with mild hepatic impairment, 1 patient with moderate hepatic impairment, and 2 patients with severe hepatic impairment. No dose adjustments are recommended for patients with mild hepatic impairment. Reduce the romidepsin injection starting dose for patients with moderate and severe hepatic impairment *[see Dosage and Administration (2.3)* and *Clinical Pharmacology (12.3)]*. Monitor patients with hepatic impairment more frequently for toxicity, especially during the first cycle of therapy.

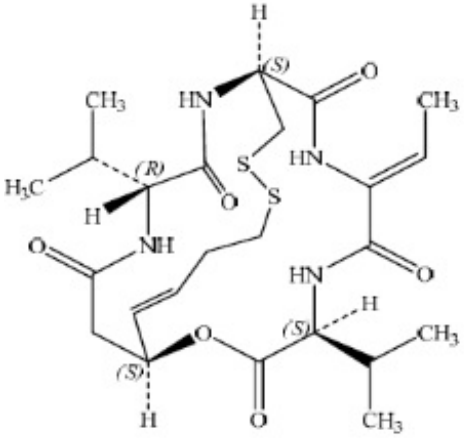
10 OVERDOSAGE

No specific information is available on the treatment of overdosage of romidepsin. Toxicities in a single-dose study in rats or dogs, at intravenous romidepsin doses up to 2.2-fold the recommended human dose based on the body surface area, included irregular respiration, irregular heartbeat, staggering gait, tremor, and tonic convulsions. In the event of an overdose, it is reasonable to employ the usual supportive measures, e.g., clinical monitoring and supportive therapy, if required. There is no known antidote for romidepsin and it is not known if romidepsin is dialyzable.

11 DESCRIPTION

Romidepsin, a histone deacetylase (HDAC) inhibitor, is a bicyclic depsipeptide. At room temperature, romidepsin is a white to off-white crystalline powder and is described chemically as (1S,4S,7Z,10S,16E,21R)-7-ethylidene-4,21-bis(1-methylethyl)-2-oxa-12,13-dithia-5,8,20,23-tetraazabicyclo[8.7.6]tricos-16-ene-3,6,9,19,22-pentone. The molecular formula is $C_{24}H_{36}N_4O_6S_2$.

The molecular weight is 540.7 g/mol and the structural formula is:



Romidepsin injection is intended for intravenous infusion only after dilution with 0.9% Sodium Chloride, USP.

Romidepsin injection is a sterile, clear, colorless to pale yellow solution and is supplied in single-dose vial.

Each mL contains romidepsin, 5 mg; povidone, 10 mg; DL-alpha-tocopherol, 0.05 mg; dehydrated alcohol, 157.8 mg (20% v/v) and propylene glycol, 828.8 mg.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Romidepsin is a histone deacetylase (HDAC) inhibitor. HDACs catalyze the removal of acetyl groups from acetylated lysine residues in histones, resulting in the modulation of gene expression. HDACs also deacetylate non-histone proteins, such as transcription factors. *In vitro*, romidepsin causes the accumulation of acetylated histones, and induces cell cycle arrest and apoptosis of some cancer cell lines with IC50 values in the nanomolar range. The mechanism of the antineoplastic effect of romidepsin observed in nonclinical and clinical studies has not been fully characterized.

12.2 Pharmacodynamics

Cardiac Electrophysiology

At doses of 14 mg/m^2 as a 4-hour intravenous infusion and at doses of 8 (0.57 times the recommended dose), 10 (0.71 times the recommended dose) or 12 (0.86 times the recommended dose) mg/m^2 as a 1-hour infusion, no large changes in the mean QTc interval (> 20 milliseconds) from baseline based on Fridericia correction method were detected. Small increase in mean QT interval (< 10 milliseconds) and mean QT interval increase between 10 to 20 milliseconds cannot be excluded.

Romidepsin was associated with a delayed concentration-dependent increase in heart rate in patients with advanced cancer with a maximum mean increase in heart rate of 20 beats per minute occurring at the 6-hour time point after start of romidepsin infusion for patients receiving 14 mg/m^2 as a 4-hour infusion.

12.3 Pharmacokinetics

In patients with T-cell lymphomas who received 14 mg/m^2 of romidepsin intravenously over a 4-hour period on days 1, 8, and 15 of a 28-day cycle, geometric mean values of the maximum plasma concentration (C_{max}) and the area under the plasma concentration versus time curve ($AUC_{0-\infty}$) were 377 ng/mL and 1,549 ng*hr/mL, respectively. Romidepsin exhibited linear pharmacokinetics across doses ranging from 1.0 (0.07 times the recommended dose) to 24.9 (1.76 times the recommended dose) mg/m^2 when administered intravenously over 4 hours in patients with advanced cancers.

Distribution

Romidepsin is highly protein bound in plasma (92% to 94%) over the concentration range of 50 ng/mL to 1,000 ng/mL with α1-acid-glycoprotein (AAG) being the principal binding protein. Romidepsin is a substrate of the efflux transporter P-glycoprotein (P-gp, ABCB1).

In vitro, romidepsin accumulates into human hepatocytes via an unknown active uptake process. Romidepsin is not a substrate of the following uptake transporters: BCRP, BSEP, MRP2, OAT1, OAT3, OATP1B1, OATP1B3, or OCT2. In addition, romidepsin is not an inhibitor of BCRP, MRP2, MDR1 or OAT3. Although romidepsin did not inhibit OAT1, OCT2, and OATP1B3 at concentrations seen clinically (1 µmol/L), modest inhibition was observed at 10 µmol/L. Romidepsin was found to be an inhibitor of BSEP and OATP1B1.

Metabolism

Romidepsin undergoes extensive metabolism *in vitro* primarily by CYP3A4 with minor contribution from CYP3A5, CYP1A1, CYP2B6, and CYP2C19. At therapeutic concentrations, romidepsin did not competitively inhibit CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4 *in vitro*.

At therapeutic concentrations, romidepsin did not cause notable induction of CYP1A2, CYP2B6 and CYP3A4 *in vitro*. Therefore, pharmacokinetic drug-drug interactions are unlikely to occur due to CYP450 induction or inhibition by romidepsin when co-administered with CYP450 substrates.

Excretion

Following 4-hour intravenous administration of romidepsin at 14 mg/m^2 on days 1, 8, and 15 of a 28-day cycle in patients with T-cell lymphomas, the terminal half-life ($t_{1/2}$) was approximately 3 hours. No accumulation of plasma concentration of romidepsin was observed after repeated dosing.

Drug Interactions

Ketoconazole

Following co-administration of 8 mg/m^2 romidepsin (4-hour infusion) with ketoconazole, the overall romidepsin exposure was increased by approximately 25% and 10% for $AUC_{0-\infty}$ and C_{max}, respectively, compared to romidepsin alone, and the difference in $AUC_{0-\infty}$ between the 2 treatments was statistically significant.

Rifampin

Following co-administration of 14 mg/m^2 romidepsin (4-hour infusion) with rifampin, the overall romidepsin exposure was increased by approximately 80% and 60% for $AUC_{0-\infty}$ and C_{max}, respectively, compared to romidepsin alone, and the difference between the 2

treatments was statistically significant. Co-administration of rifampin decreased the romidepsin clearance and volume of distribution by 44% and 52%, respectively. The increase in exposure seen after co-administration with rifampin is likely due to rifampin's inhibition of an undetermined hepatic uptake process that is predominant for the disposition of romidepsin.

Drugs that inhibit P-glycoprotein

Drugs that inhibit p-glycoprotein may increase the concentration of romidepsin.

Specific Populations

Effect of Age, Gender, Race or Renal Impairment

The pharmacokinetics of romidepsin was not influenced by age (27 years to 83 years), gender, race (white vs. black) or mild (estimated creatinine clearance 50 mL/min to 80 mL/min), moderate (estimated creatinine clearance 30 mL/min to 50 mL/min), or severe (estimated creatinine clearance < 30 mL/min) renal impairment. The effect of end-stage renal disease (estimated creatine clearance less than 15 mL/min) on romidepsin pharmacokinetics has not been studied.

Hepatic Impairment

Romidepsin clearance decreased with increased severity of hepatic impairment. In patients with cancer, the geometric mean C_{max} values after administration of 14, 7, and 5 mg/m^2 romidepsin in patients with mild (B1: bilirubin ≤ ULN and AST > ULN; B2: bilirubin > ULN but ≤ 1.5 × ULN and any AST), moderate (bilirubin > 1.5 × ULN to ≤ 3 × ULN and any AST), and severe (bilirubin > 3 × ULN and any AST) hepatic impairment were approximately 111%, 96%, and 86% of the corresponding value after administration of 14 mg/m^2 romidepsin in patients with normal (bilirubin ≤ upper limit of normal (ULN) and aspartate aminotransferase (AST) ≤ ULN) hepatic function, respectively. The geometric mean AUC_{inf} values in patients with mild, moderate, and severe hepatic impairment were approximately 144%, 114%, and 116% of the corresponding value in patients with normal hepatic function, respectively. Among these 4 cohorts, moderate interpatient variability was noted for the exposure parameters C_{max} and AUC_{inf}, as the coefficient of variation (CV) ranged from 30% to 54%.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been performed with romidepsin. Romidepsin was not mutagenic *in vitro* in the bacterial reverse mutation assay (Ames test) or the mouse lymphoma assay. Romidepsin was not clastogenic in an *in vivo* rat bone marrow micronucleus assay when tested to the maximum tolerated dose (MTD) of 1 mg/kg in males and 3 mg/kg in females (6 and 18 mg/m^2 in males and females, respectively). These doses were up to 1.3-fold the recommended human dose, based on body surface area.

Based on nonclinical findings, male and female fertility may be compromised by treatment with romidepsin. In a 26-week toxicology study, romidepsin administration resulted in testicular degeneration in rats at 0.33 mg/kg/dose (2 mg/m^2/dose) following the clinical dosing schedule. This dose resulted in $AUC_{0-\infty}$ values that were approximately

2% the exposure level in patients receiving the recommended dose of 14 mg/m^2/dose. A similar effect was seen in mice after 4 weeks of drug administration at higher doses. Seminal vesicle and prostate organ weights were decreased in a separate study in rats after 4 weeks of daily drug administration at 0.1 mg/kg/day (0.6 mg/m^2/day), approximately 30% the estimated human daily dose based on body surface area. Romidepsin showed high affinity for binding to estrogen receptors in pharmacology studies. In a 26-week toxicology study in rats, atrophy was seen in the ovary, uterus, vagina and mammary gland of females administered doses as low as 0.1 mg/kg/dose (0.6 mg/m^2/dose) following the clinical dosing schedule. This dose resulted in $AUC_{0-\infty}$ values that were 0.3% of those in patients receiving the recommended dose of 14 mg/m^2/dose. Maturation arrest of ovarian follicles and decreased weight of ovaries were observed in a separate study in rats after 4 weeks of daily drug administration at 0.1 mg/kg/day (0.6 mg/m^2/day). This dose is approximately 30% the estimated human daily dose based on body surface area.

14 CLINICAL STUDIES

Romidepsin was evaluated in 2 multicenter, single-arm clinical studies in patients with CTCL (Study 1 [NCT00106431] and Study 2 [NCT00007345]). Overall, 167 patients with CTCL were treated in the US, Europe, and Australia. Study 1 included 96 patients with confirmed CTCL after failure of at least 1 prior systemic therapy. Study 2 included 71 patients with a primary diagnosis of CTCL who received at least 2 prior skin directed therapies or one or more systemic therapies. Patients were treated with romidepsin at a starting dose of 14 mg/m^2 infused over 4 hours on days 1, 8, and 15 every 28 days.

In both studies, patients could be treated until disease progression at the discretion of the investigator and local regulators. Objective disease response was evaluated according to a composite endpoint that included assessments of skin involvement, lymph node and visceral involvement, and abnormal circulating T-cells (“Sézary cells”).

The primary efficacy endpoint for both studies was overall objective disease response rate (ORR) based on the investigator assessments, and was defined as the proportion of patients with confirmed complete response (CR) or partial response (PR). CR was defined as no evidence of disease and PR as ≥ 50% improvement in disease. Secondary endpoints in both studies included duration of response and time to response.

Baseline Patient Characteristics

Demographic and disease characteristics of the patients in Study 1 and Study 2 are provided in Table 3.

Table 3: Baseline Patient Characteristics (CTCL Population)

Characteristic	**Study 1 (N = 96)**	**Study 2 (N = 71)**
Age		
N	96	71
Mean (SD)	57 (12)	56 (13)
Median (Range)	57 (21, 89)	57 (28, 84)
Sex, n (%)		
Men	59 (61)	48 (68)

Women	37 (39)	23 (32)
Race, n (%)		
White	90 (94)	55 (77)
Black	5 (5)	15 (21)
Other/Not Reported	1 (1)	1 (1)
Stage of Disease at Study Entry, n (%)		
IA	0 (0)	1 (1)
IB	15 (16)	6 (9)
IIA	13 (14)	2 (3)
IIB	21 (22)	14 (20)
III	23 (24)	9 (13)
IVA	24 (25)	27 (38)
IVB	0 (0)	12 (17)
Number of Prior Skin-Directed Therapies		
Median (Range)	2 (0, 6)	1 (0, 3)
Number of Prior Systemic Therapies		
Median (Range)	2 (1, 8)	2 (0, 7)

Clinical Results

Efficacy outcomes for CTCL patients are provided in Table 4. Median time to first response was 2 months (range 1 to 6) in both studies. Median time to CR was 4 months in Study 1 and 6 months in Study 2 (range 2 to 9).

Table 4: Clinical Results for CTCL Patients

Response Rate	**Study 1 (N = 96)**	**Study 2 (N = 71)**
ORR (CR + PR), n (%) [95% Confidence Interval]	33 (34) [25, 45]	25 (35) [25, 49]
CR, n (%) [95% Confidence Interval]	6 (6) [2, 13]	4 (6) [2, 14]
PR, n (%) [95% Confidence Interval]	27 (28) [19, 38]	21 (30) [20, 43]
Duration of Response (months)		
N	33	25
Median (range)	15 (1, 20*)	11 (1, 66*)
*Denotes censored value.		

15 REFERENCES

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

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

Romidepsin Injection is supplied as a sterile, clear, colorless to pale yellow solution available in single-dose vial in the following carton packaged strength.

27.5 mg/5.5 mL (5 mg/mL)

1 Single-Dose Vial in 1 Carton: NDC 70121-2250-1

Storage and Handling

Store at 20° to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° to 86°F) in the carton [see USP Controlled Room Temperature]. Protect from light.

Romidepsin injection 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).

Low Blood Counts

Advise patients that treatment with romidepsin injection can cause low blood counts and that frequent monitoring of hematologic parameters is required. Patients should be instructed to report fever or other signs of infection, significant fatigue, shortness of breath, or bleeding *[see Warnings and Precautions (5.1)]*.

Infections

Advise patients that infections may occur during treatment with romidepsin injection. Advise patients to report fever, cough, shortness of breath with or without chest pain, burning on urination, flu-like symptoms, muscle aches, or worsening skin problems. Advise patients to report any previous history of hepatitis B before starting romidepsin injection *[see Warnings and Precautions (5.2)]*.

Tumor Lysis Syndrome

Advise patients of the risk of tumor lysis syndrome (especially those with advanced stage disease and/or high tumor burden) to maintain high fluid intake for at least 72 hours after each dose *[see Warnings and Precautions (5.4)]*.

Nausea and Vomiting

Advise patients that nausea and vomiting are common following treatment with romidepsin injection. Prophylactic antiemetics are recommended for all patients. Advise patients to report these symptoms so that appropriate treatment can be instituted *[see Adverse Reactions (6.1)]*.

Embryo-Fetal Toxicity

Advise patients that romidepsin injection can cause fetal harm when administered during pregnancy *[see Warnings and Precautions (5.5)* and *Use in Specific Populations (8.1)]*.

Contraception

Advise females of reproductive potential to use effective contraception during treatment with romidepsin injection and for 1 month after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with romidepsin injection and for 1 month after the last dose *[Use in Specific Populations*

(8.3)].

Lactation

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

Infertility

Advise females and males of reproductive potential that romidepsin injection may cause infertility *[see Nonclinical Toxicology (13.1)]*.

Manufactured by:

Amneal Oncology Pvt. Ltd.

Telangana 509301, INDIA

Distributed by:

Amneal Pharmaceuticals LLC

Bridgewater, NJ 08807

Rev. 09-2025-00

PATIENT INFORMATION

Romidepsin (roe" mi dep' sin) Injection
For Intravenous Use

What is romidepsin injection?

Romidepsin injection is a prescription medicine used to treat adults with a type of cancer called cutaneous T-cell lymphoma (CTCL) after at least one other type of medicine by mouth or injection has been tried.
It is not known if romidepsin injection is safe and effective in children.

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

- have any heart problems, including an irregular or fast heartbeat, or a condition called QT prolongation.
- have liver problems, including a history of hepatitis B
- have problems with the amount of potassium or magnesium in your blood
- are pregnant or plan to become pregnant. Romidepsin injection can harm your unborn baby.

- **Females who are able to become pregnant:**

- Your healthcare provider will perform a pregnancy test within 7 days before you start treatment with romidepsin injection.
- You should avoid becoming pregnant during treatment with romidepsin injection and for 1 month after the last dose.
- You should use effective birth control (contraception) during treatment with

romidepsin injection and for 1 month after your last dose.
- Romidepsin injection may affect the way estrogen-containing birth control works. Talk to your healthcare provider for information about other types of birth control to use during treatment with romidepsin injection.
- Tell your healthcare provider right away if you become pregnant or think you may be pregnant during treatment with romidepsin injection.

- **Males with a female partner who can become pregnant:**

- Romidepsin injection can harm the unborn baby of your partner.
- You should use effective birth control (contraception) and avoid fathering a child during treatment with romidepsin injection and for 1 month after the last dose. Talk to your healthcare provider if this is a concern for you.

- **Romidepsin injection may cause fertility problems in males and females. Talk to your healthcare provider if this is a concern for you.**

- are breastfeeding or plan to breastfeed. It is not known if romidepsin passes into your breast milk. You should not breastfeed during treatment with romidepsin injection and for 1 week after the last dose. Talk to your healthcare provider about the best way to feed your baby while you are being treated with romidepsin injection.

Tell your healthcare provider about all of the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Some medicines may affect how romidepsin injection works, or romidepsin injection may affect how other medicines work. Especially tell your healthcare provider if you take or use:
- warfarin sodium (Coumadin, Jantoven) or any other blood thinner medicine. Ask your healthcare provider if you are not sure if you are taking a blood thinner. Your healthcare provider may want to test your blood more often.
- a medicine to treat abnormal heartbeats
- St. John's wort (*Hypericum perforatum*)
- Dexamethasone (a steroid)

- Medicine for:

- tuberculosis (TB)
- seizures (epilepsy)
- bacterial infections (antibiotics)
- fungal infections (antifungals)
- HIV (AIDS)
- depression

Know the medicines you take. Keep a list of them and show it to your healthcare provider and pharmacist when you get a new medicine.

How will I receive romidepsin injection?

- Romidepsin injection will be given to you by your healthcare provider or nurse as an intravenous injection into your vein usually over 4 hours.

- Romidepsin injection is usually given on Day 1, Day 8, and Day 15 of a 28-day cycle of treatment.
- Your healthcare provider will decide how long you will receive treatment with romidepsin injection.
- Your healthcare provider may decrease your dose, or delay or stop your treatment with romidepsin injection if you have certain side effects.

What are the possible side effects of romidepsin injection?

Romidepsin injection may cause serious side effects, including:

- **Low blood cell counts.** Your healthcare provider will regularly do blood tests during treatment with romidepsin injection to check your blood counts. Tell your healthcare provider if you have signs or symptoms of:

  - **Low platelets:** can cause unusual bleeding or bruising under the skin.
  - **Low red blood cells:** may make you feel tired and you may get tired easily.
  - **Low white blood cells:** can cause you to get infections, which may be serious.

- **Serious infections.** People receiving romidepsin injection can develop serious infections that can sometimes lead to death. These infections can happen during and after treatment with romidepsin injection. Your risk of infection may be higher if you have had chemotherapy in the past. Tell your healthcare provider right away if you have any of these symptoms of infection:

◦ fever	◦ burning with urination
◦ cough	◦ flu-like symptoms
◦ shortness of breath with or without chest pain	◦ muscle aches
	◦ worsening skin problems

- **Changes in your heartbeat.** Your healthcare provider may check your heart by doing an ECG (electrocardiogram) and will do blood tests to check your potassium and magnesium levels before you start treatment with romidepsin injection. Tell your healthcare provider if you feel an abnormal heartbeat, feel dizzy or faint, have chest pain or shortness of breath.

- **Tumor Lysis Syndrome (TLS).** TLS is a problem of the rapid breakdown of cancer cells that can happen during your treatment with romidepsin injection. You should drink plenty of fluids for at least 3 days after each dose of romidepsin injection. Your healthcare provider may do blood tests to check for TLS and may give you medicine to prevent or treat TLS.
  The most common side effects of romidepsin injection include:

- nausea, tiredness, vomiting, loss of appetite, changes in sense of taste, constipation, and itching.

Tell your healthcare provider if you have nausea or vomiting during treatment with romidepsin injection. Your healthcare provider will treat your symptoms and may give you medicines before your dose of romidepsin injection to help prevent nausea and vomiting.
These are not all the possible side effects of romidepsin injection.
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 romidepsin injection.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet.
This Patient Information leaflet summarizes the most important information about romidepsin injection. You can ask your pharmacist or healthcare provider for information about romidepsin injection that is written for health professionals.

What are the ingredients in romidepsin injection?
Active ingredient: romidepsin
Inactive ingredients: povidone, DL-alpha-tocopherol, dehydrated alcohol and propylene glycol.

Brands listed are the trademarks of their respective owners.

For more information, go to www.amneal.com or call 1-877-835-5472.

This Patient Information has been approved by the U.S. Food and Drug Administration.

Manufactured by:
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Telangana 509301, INDIA

Distributed by:
Amneal Pharmaceuticals LLC
Bridgewater, NJ 08807

Rev. 09-2025-00

PRINCIPAL DISPLAY PANEL

NDC 70121-2250-1

Romidepsin Injection, 27.5 mg/5.5 mL (5 mg/mL)

For Intr**avenous Infusion After Dilution Only**

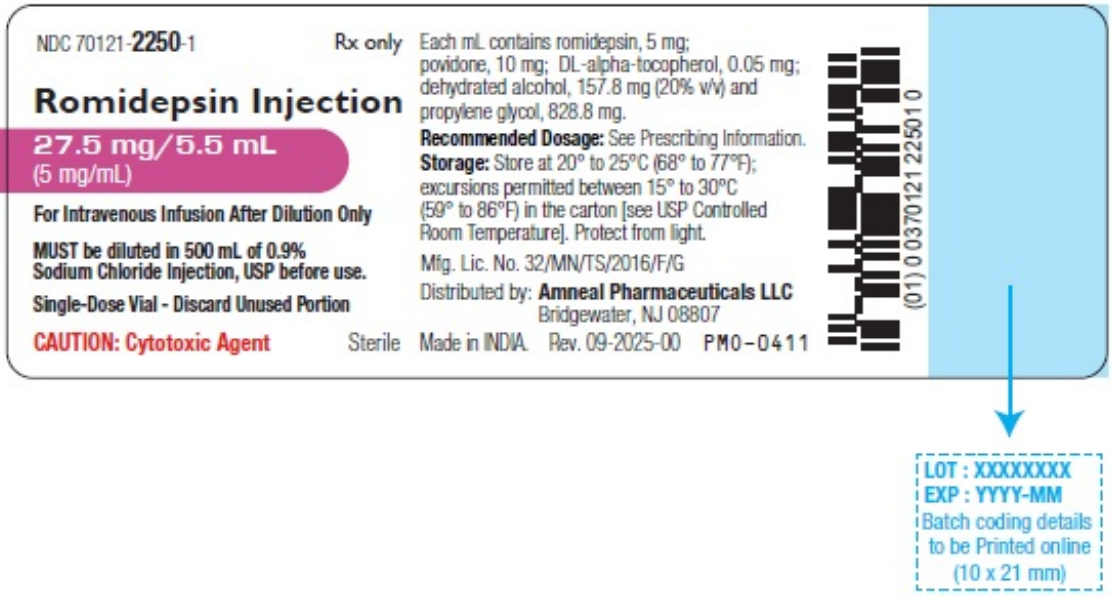
MUST be diluted in 500 mL of 0.9%

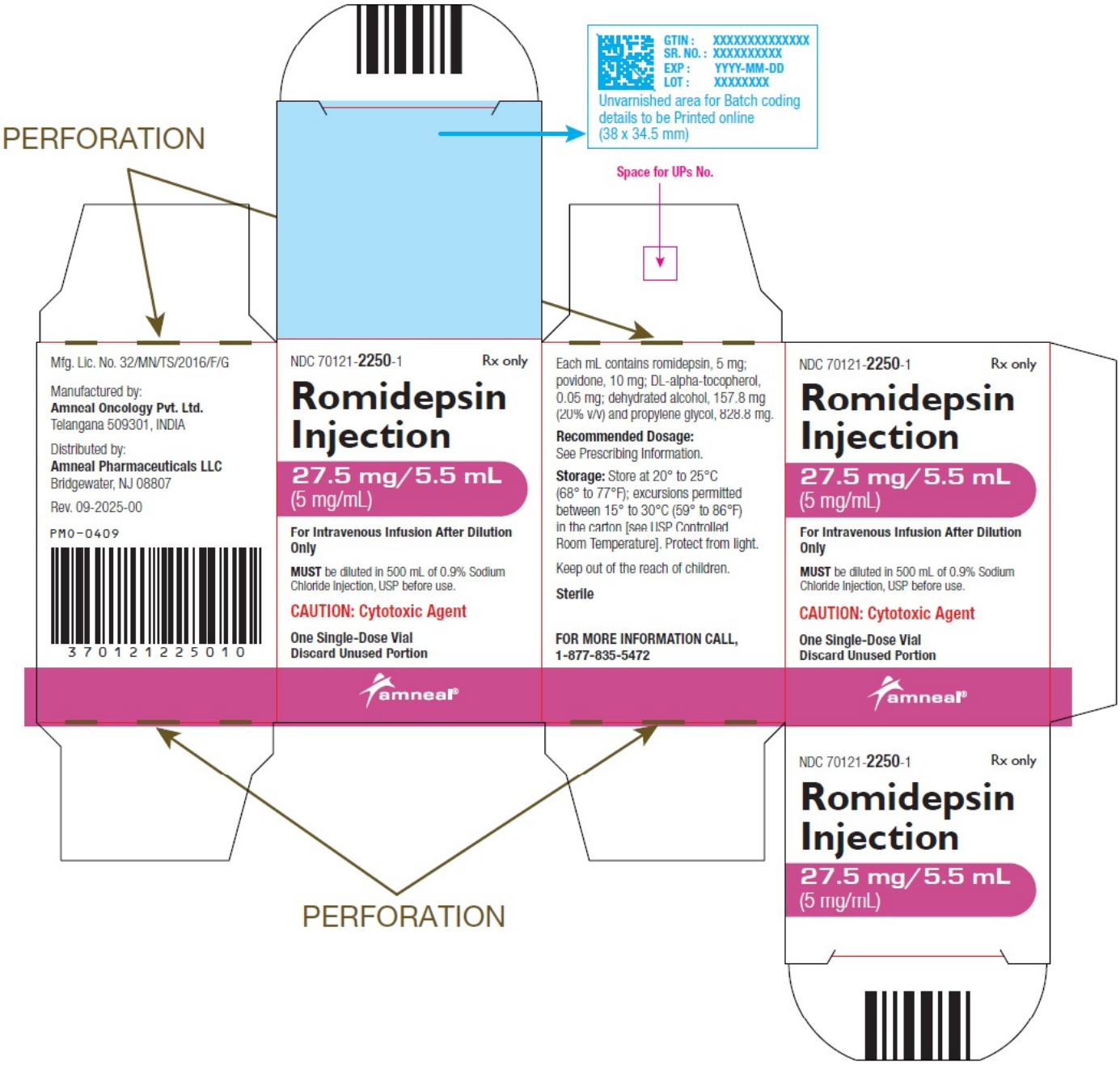
Sodium Chloride Injection, USP before use.

Single-Dose Vial - Discard Unused Portion

CAUTION: Cytotoxic Agent

Sterile





ROMIDEPSIN

romidepsin injection, solution, concentrate

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:70121-2250
Route of Administration	INTRAVENOUS		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
ROMIDEPSIN (UNII: CX3T89XQBK) (ROMIDEPSIN - UNII:CX3T89XQBK)	ROMIDEPSIN	5 mg in 1 mL

Inactive Ingredients

Ingredient Name	Strength
POVIDONE K17 (UNII: C67P1734QJ)	
.ALPHA.-TOCOPHEROL, DL- (UNII: 7QWA1RIO01)	
ALCOHOL (UNII: 3K9958V90M)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:70121-2250-1	1 in 1 CARTON	06/02/2026	
1		5.5 mL in 1 VIAL; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA219099	06/02/2026	

Labeler - Amneal Pharmaceuticals LLC (827748190)

Establishment

Name	Address	ID/FEI	Business Operations
Amneal Oncology Private Limited		860037948	analysis(70121-2250) , label(70121-2250) , manufacture(70121-2250) , pack(70121-2250) , sterilize(70121-2250)

Revised: 9/2025 Amneal Pharmaceuticals LLC