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Romidepsin For Injection

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ROMIDEPSIN FOR INJECTION safely and effectively See full prescribing information for ROMIDEPSIN FOR

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

—— INDICATIONS AND USAGE ——

Romidepsin for 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

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

- 14 mg/m² 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 · Discontinue or interrupt treatment (with or without dose reduc-
- tion to 10 mg/m²) to manage drug toxicity (2.2).
- · Reduce starting dose in patients with moderate and severe hepatic impairment (2.3).

— DOSAGE FORMS AND STRENGTHS ———

For injection: 10 mg of romidepsin as a lyophilized powder in single-dose vial for reconstitution (3).

— CONTRAINDICATIONS ———

None (4).

WARNINGS AND PRECAUTIONS —

- Myelosuppression: romidepsin can cause thrombocytopenia, eukopenia (neutropenia and lymphopenia), and anemia; monitor blood counts during treatment with romidepsin; 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).

- <u>Electrocardiographic (ECG) changes:</u> Consider cardiovascular nonitoring 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 (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 labora-

tory abnormalities, are nausea, fatigue, infections, vomiting anorexia, electrocardiogram ST-T wave changes, dysgeusia constipation and pruritus. Grade 3-4 laboratory abnormalities (≥10%) include lymphopenia, neutropenia, anemia and thromocytopenia (6)

To report SUSPECTED ADVERSE REACTIONS, contact Fresenius Kabi USA, LLC at 1-800-551-7176 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

- Normalized Ratio (INR) in patients concurrently administered romidepsin and warfarin or coumarin derivatives (7.1). Monitor for toxicities related to increased romidepsin exposure

8.3 Females and Males of Reproductive Potential

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FULL PRESCRIBING INFORMATION

INDICATIONS AND USAGE Romidepsin for injection is indicated for the treatment of cutaneous

T-cell lymphoma (CTCL) in adult patients who have received at least one prior systemic therapy. DOSAGE AND ADMINISTRATION

2.1 Dosage Information

he recommended dosage of romidepsin is 14 mg/m² 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 romidensin should be delayed

- until toxicity returns to Grade 0-1 or baseline, then therapy may be restarted at 14 mg/m². If Grade 3 toxicity recurs, treatment with romidepsin should be delayed until toxicity returns to Grade 0-1 or baseline and the dose should be permanently reduced to 10 mg/m Grade 4 toxicity: Treatment with romidepsin should be delaye until toxicity returns to Grade 0-1 or baseline, then the dose should
- be permanently reduced to 10 mg/m² Romidensin should be discontinued if Grade 3 or 4 toxicities recur
- Grade 3 or 4 neutropenia or thrombocytopenia: Treatment with romidepsin should be delayed until the specific cytopenia returns

DRUG INTERACTIONS Carefully monitor prothrombin time (PT) and International

when co-administering romidepsin with strong CYP3A4 inhibi-· Avoid use with rifampin and strong CYP3A4 inducers (7.3). See 17 for PATIENT COUNSELING INFORMATION and

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- to ANC greater than or equal to 1.5×109/L and platelet count greater than or equal to 75×10⁹/L or baseline, then therapy may be restarted at 14 mg/m².
- Grade 4 febrile (greater than or equal to 38.5°C) neutropenia or thrombocytopenia that requires platelet transfusion: Treatment with romidepsin should be delayed until the specific cytopeni returns to less than or equal to Grade 1 or baseline, and then the dose should be permanently reduced to 10 mg/m

Dosage in Patients with Hepatic Impairment

the starting dose of Romidepsin for 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

epatic Impairment	Bilirubin Levels	injection Dose			
Moderate	greater than 1.5 x ULN to less than or equal to 3 x ULN	7 mg/m ²			
Severe	greater than 3 x ULN	5 mg/m ²			
ULN=Upper limit of normal.					

Instructions for Preparation and Intravenous Administration nidepsin for injection is a hazardous drug. Use appropriate handling procedures.1

- Romidepsin for injection must be reconstituted with the supplied diluent and further diluted with 0.9% Sodium Chloride Injection, USP before intravenous infusion. Romidepsin for injection and diluent vials contain an overfill to ensure the recommended volume can be withdrawn at a concentration of 5 mg/mL.
- Each 10 mg single-dose vial of Romidepsin for injection must be reconstituted with 2.2 mL of the supplied diluent.
- With a suitable syringe, asentically withdraw 2.2 ml, from the injection vial. Swirl the contents of the vial until there are no visible contain romidepsin for injection 5 mg/mL. The reconstituted Romidepsin for injection vial will contain 2 mL of deliverable volume of drug product. The reconstituted Romidepsin for injection solution is chemically stable for up to 8 hours at room temperature Extract the appropriate amount of Romidensin for injection from the
- vials to deliver the desired dose, using proper aseptic technique. Before intravenous infusion, further dilute Romidensin for injection in 500 mL 0.9% Sodium Chloride Injection, USP. Infuse over 4 hours

The diluted solution is compatible with polyvinyl chloride (PVC), ethylene vinyl acetate (EVA), polyethylene (PÉ) 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 or Injection: 10 mg of romidepsin as a lyophilized white powder in a single-dose vial for reconstitution and further dilution. CONTRAINDICATIONS

DOSAGE FORMS AND STRENGTHS

- - WARNINGS AND PRECAUTIONS

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

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 lifethreatening 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)

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

Reactivation of hepatitis B virus infection was reported in 1% of

has occurred in recipients of romidepsin including after ganciclovir

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 Isee Adverse Reactions (6.1)1.

n patients with congenital long QT syndrome, patients with a history of significant cardiovascular disease, and patients taking anti hythmic medicines or medicinal products that lead to sign QT prolongation, consider cardiovascular monitoring of ECGs at

Confirm that potassium and magnesium levels are within normal range before administration of romidepsin [see Adverse Reactions

5.4 Tumor Lysis Syndrome

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

5.5 Embryo-Fetal Toxicity
Based on its mechanism of action and findings from animal studies romidepsin can cause fetal harm when administered to a pregnant woman. In an animal reproductive study, romidepsin was embryocida and caused adverse developmental outcomes at exposures below those in patients at the recommended dose of 14 mg/m². Advise females of reproductive potential to use effective contraception during treatment and for 1 month after the last dose. Advise males with emale partners of reproductive potential to use effective contraception during treatment and for 1 month after the last dose [see] lse in Specific Populations (8.1, 8.3) and Clinical Pharmacology (12.1)].

ADVERSE REACTIONS

exposed for greater than one year.

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

 Mvelosuppression (see Warnings and Precautions (5.1)) Infections [see Warnings and Precautions (5.2)] • Electrocardiographic Changes [see Warnings and Precautions

• Tumor Lysis Syndrome [see Warnings and Precautions (5.4)] 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 nistered as a single agent at a dosage of 14 mg/m2 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

Cutaneous T-Cell Lymphoma

Table 2 summarizes the most frequent adverse reactions (>20%)

regardless of causality using the National Cancer Institute-Commo 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

Table 2. Adverse Reactions

Occurring in >20% of Patients in Either CTCL Study (N=185)

Study 1 (n=102)

All Grade 3

22 (22)

20 (20)

19 (19)

17 (17)

15 (15)

12 (12)

11 (11)

7 (7)

7 (7)

6 (6)

4 (4)

4 (4)

3 (3)

3 (3)

3 (3)

2(2)

ommonly reported (>20%) as adverse reactions are included in

Study 2 (n=83)

All grades

99 (97) 36 (35) 83 (100) 68 (82)

54 (53) 8 (8) 64 (77) 12 (14)

1 (<1) 23 (28)

1 (<1) 22 (27)

0 54 (65)

0 33 (40)

2 (2) 32 (39)

3 (3) 19 (23)

0 26 (31)

0 17 (20)

1 (<1) 22 (27)

4 (4) 0 43 (52) 5 (6)

0 47 (57)

1 (<1) 40 (48)

1 (<1) 1 (<1) 17 (20) 2 (2)

0 0 27 (33) 7 (8)

18 (22)

23 (28)

52 (63)

42 (51)

4 (4) 0 38 (46)

0

0

2 (2)

0 0 22 (27)

0 0 22 (27)

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%)

thrombocytopenia, nausea, leukopenia, dehydration, pyrexia, aspai

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

o infection and one each due to myocardial ischemia and acute

ontinuation due to an adverse event occurred in 21% of patients

of patients in either study included infection, fatigue, dyspnea,

in Study 1 and 11% in Study 2. Discontinuations occurring in at least

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 significan

9%), dyspnea (15%), abdominal pain (13%) and stomatitis (10%)

adverse reactions included dysgeusia (22%), headache (20%), cough

Grade 3 and higher adverse reactions in ≥10% were hematologic

toxicities (including thrombocytopenia, neutropenia, leukopenia and

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

te aminotransferase increased, sepsis, catheter related infection,

60 (72)

4 (4) 47 (57) 22 (27)

57 (56) 3 (3) 71 (86)

47 (46) 11 (11) 45 (54)

35 (34) 1 (<1) 43 (52)

23 (23) 1 (<1) 45 (54)

20 (20) 4 (4) 19 (23)

3 (3)

Grade 3

5 (6)

27 (33)

12 (14)

3 (4)

5 (6)

7 (8)

2(2)

3 (4)

(range: <1 to 83.4 months).

Common Adverse Reactions

dverse Reactions n (%)

Any adverse reactions

Asthenia/Fatique

ypomagnesemi

rombocytonen

onstination

Pruritus

vnokalemia

/pocalcemia

eukopenia

ymphopenia

nine aminotransferase

Aspartate aminotransferase

/poalbuminemia

vave changes

yperglycemia

ypermagnesemia

Serious Adverse Reactions

hypophosphatemia and dyspnea (4%).

QT prolongation, and hypomagnesemia.

respiratory distress syndrome.

Other Clinical Trials Experience

anemia) and fatique

DRUG INTERACTIONS

Warfarin or Coumarin Derivatives

and warfarin [see Clinical Pharmacology (12.3)].

lermatitis

ermatitis/Exfoliation

Pvrexia

Drugs That Inhibit CYP3A4 Enzymes he safety of romidepsin was evaluated in 185 patients with CTCL ir ong CYP3A4 inhibitors increase concentrations of romidensin (see 2 single arm clinical studies in which patients received a dosage of 14 mg/m² on days 1, 8, and 15 of a 28-day cycle. Treatment continued Clinical Pharmacology (12.3)]. Monitor for toxicity related to increased romidensin exposure and follow the dose modifications for toxicity as long as the patient benefitted from and tolerated the drug The mean duration of treatment in these studies was 5.6 months see Dosage and Administration (2.2)] when romidepsin is initially co-administered with strong CYP3A4 inhibitors. 7.3 Drugs That Induce CYP3A4 Enzymes

noin (a potent CYP3A4 inducer) increased the concentrations

of romidepsin [see Clinical Pharmacology (12.3)]. Avoid co-adm istration of romidensin with rifampin. The use of other potent CYP3A4 inducers should be avoided when possible.

USE IN SPECIFIC POPULATIONS

8.1

Based on its mechanism of action and findings from animal studies romidepsin 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 backround risk of birth defect, loss, or other adverse outcomes. In the J.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Romidensin 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 expo recommended dose of 14 mg/m²/week. Drug-related fetal effects onsisted of reduced fetal body weights, folded retina, rotated limbs and incomplete sternal ossification

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 pecause of the potential for serious adverse reactions in the breastfed child, advise lactating women not to breastfeed during treatment with midepsin and for 1 week after the last dose. Females and Males of Reproductive Potential

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

<u>Pregnancy Testing</u> <u>Perform pregnancy testing in females of reproductive potential within</u> 7 days prior to initiating therapy with romidepsin

Contraception

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

Advise males with female partners of reproductive potential to use

effective contraception during treatment with romidepsin and for 1 month after the last dose. Based on findings in animals, romidensin has the potential to affect

Pediatric Use The safety and effectiveness of romidepsin in pediatric patients have

not been established.

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 of age and over and younge

patients: however, greater sensitivity of some older individuals cannot

male and female fertility [see Nonclinical Toxicology (13.1)].

be ruled out. 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 nild hepatic impairment. Reduce the romidepsin 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.

OVERDOSAGE

known if romidepsin is dialyzable.

No specific information is available on the treatment of overdosage of romidepsin. Toxicities in a single-dose study in rats or dogs, at intravenous

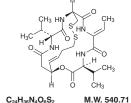
romidepsin doses up to 2.2-fold the recommended human dose pased on the body surface area, included irregular respiration, irregular heartbeat, staggering gait, tremor, and tonic convulsions. In the event of an overdose, it is reasonable to employ the usual

supportive measures, e.g., clinical monitoring and supportive therapy, if required. There is no known antidote for romidepsin and it is not

DESCRIPTION

Romidensin, a histone deacetylase (HDAC) inhibitor, is a bicyclic depsipeptide. At room temperature, romidepsin is a white powder and is described chemically as (1S.4S.7Z.10S.16E.21R)-7-ethylidenecvclo[8.7.6]tricos-16-ene-3,6,9,19,22-pentone.

The structural formula is:



Romidepsin for injection is intended for intravenous infusion only after

reconstitution with the supplied diluent and after further dilution with 0.9% Sodium Chloride, USP. Romidepsin is supplied as a kit containing 2 vials.

Romidepsin for injection is a sterile lyophilized white powder and is supplied in a 10 mg single-dose vial containing 11 mg romidepsin, 22 mg povidone, USP, and hydrochloric acid, NF, as a pH adjuster.

Diluent for romidensin is a sterile clear solution and is supplied in a single-dose vial with 2.2 mL deliverable volume. Diluent for romidepsin contains 80% (v/v) propylene glycol, USP and 20% (v/v) dehydrated alcohol, USP.

12 CLINICAL PHARMACOLOGY 12.1 Mechanism of Action

idepsin is a histone deacetylase (HDAC) inhibitor. HDACs catalyze the removal of acetyl groups from acetylated lysine residues in ones, resulting in the modulation of gene expression. HDACs also deacetylate non-histone proteins, such as transcription factors. n vitro, romidepsin causes the accumulation of acetylated histones and induces cell cycle arrest and apoptosis of some cancer cel lines with ${\rm IC}_{50}$ 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/m² 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/m² as 1-hour infusion, no large changes in the mean QTc interval (>20 milliseconds) from baseline based on Fridericia correction method vere detected. Small increase in mean QT interval (< 10 millised onds) and mean QT interval increase between 10 to 20 milliseconds

Romidensin was associated with a delayed concentration-depen

lent increase in heart rate in patients with advanced cancer with

urring at the 6-hour time point after start of romidepsin infusion

a maximum mean increase in heart rate of 20 beats per minute

for patients receiving 14 mg/m² as a 4-hour infusion. 12.3 Pharmacokinetics

In patients with T-cell lymphomas who received 14 mg/m² or epsin 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...}) were 377 ng/mL and 1549 ng*hr/mL, respectively. Romidepsin exhibited linear pharmacokinetics across doses ranging from 1.0 (0.07 times the recommended dose) to 24.9 intravenously over 4 hours in patients with advanced cancers.

Romidepsin is highly protein bound in plasma (92% to 94%) over the concentration range of 50 ng/mL to 1000 ng/mL with α 1-acidglycoprotein (AAG) being the principal binding protein. Romidensi s a substrate of the efflux transporter P-glycoprotein (P-gp, ABCB1)

In vitro, romidensin accumulates into human henatocytes via ar

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 romidensin did not inhibit OAT1, OCT2, and OATP1B3 at concentrations seen clinically (1 µmol/L), modest inhibition was observed at 10 µmol/L. Romidensing was found to be an inhibitor of BSEP and OATP1B1.

Metabolism

CYP3A4 with minor contribution from CYP3A5, CYP1A1, CYP2B6, and CYP2C19. At therapeutic concentrations, romidepsin did not competitively inhibit CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, At the ranguitic concentrations, romidens in did not cause notable

induction of CYP1A2, CYP2B6 and CYP3A4 in vitro. Therefore,

Following 4-hour intravenous administration of romidensin a

14 mg/m² on days 1, 8, and 15 of a 28-day cycle in patients with

-cell lymphomas, the terminal half-life (t.,) was approximately

3 hours. No accumulation of plasma concentration of romidepsin was

pharmacokinetic drug-drug interactions are unlikely to occur due to CYP450 induction or inhibition by romidepsin when co-administered with CYP450 substrates.

observed after repeated dosing. Drug Interactions

Ketoconazole: Following co-administration of 8 mg/m² romidepsin (4-hour infusion) with ketoconazole, the overall romidepsin exposure was increased by approximately 25% and 10% for AUC_{0-x} and C_{max} respectively, compared to romidepsin alone, and the difference in AUC between the 2 treatments was statistically significant.

Rifampin: Following co-administration of 14 mg/m² 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

What is romidepsin for injection?

Romidepsin for injection is a prescription medicine used to treat people 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.

under 18 years of age.

about all of your medical conditions, including if you: have any heart problems, including an irregular or fast heartbeat, or a

- 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 for injection may
- harm your unborn baby. Females who are able to become pregnant: Your healthcare provider will perform a pregnancy test within
- You should avoid becoming pregnant during treatment with romidepsin for injection and for 1 month after the last dose.
- treatment with romidepsin for injection and for I month after your last dose. Romidepsin for injection may affect the way estrogen-containing
- information about other types of birth control to use during treatment with romidepsin for injection. Tell your healthcare provider right away if you become pregnant or

birth control works. Talk to your healthcare provider for more

- Males with a female sexual partner who can become pregnant: Romidepsin for injection can harm the unborn baby of your partner. You should use a condom and avoid fathering a child during
- provider if this is a concern for you.
- 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 for injection passes into your breast milk. You should not breastfeed during treatment with romidepsin and for 1 week after the last dose. Talk to your

Tell your healthcare provider about all of the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal sunnlements Some medicines may affect how romidepsin for injection works, or

romidepsin for 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 (epilepsv) 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.

PATIENT INFORMATION

Romidepsin for Injection (ROĖ mi DEP sin)

It is not known if romidepsin for injection is safe and effective in children

Before receiving romidepsin for injection, tell your healthcare provider

- condition called QT prolongation. have kidney problems
- have nausea, vomiting, or diarrhea
 - 7 days before you start treatment with romidepsin for injection.
- You should use effective birth control (contraception) during
- think you may be pregnant during treatment with romidepsin for
- treatment with romidepsin for injection and for 1 month after treatment with romidepsin for injection. Talk to your healthcare
- Romidepsin for injection may cause fertility problems in males and
- healthcare provider about the best way to feed your baby while you are being treated with romidepsin for injection.

How will I receive romidepsin for injection?

- Romidepsin for injection will be given to you by your healthcare provider or nurse as an intravenous injection into your vein usually over 4 hours.
- Romidepsin for 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 for injection.
- Your healthcare provider will check your blood cell counts and other blood tests regularly during your treatment with romidepsin for injection to check for side effects of romidepsin for injection. Your healthcare provider may decide to do other tests to check your health as needed.
- Your healthcare provider may stop your treatment, change when you get your treatment, or change the dose of your treatment if you have certain side effects while receiving romidepsin for injection.

What are the possible side effects of romidepsin for injection? Romidepsin for injection may cause serious side effects, including:

- Low blood cell counts: Your healthcare provider will regularly do blood tests to check your blood counts.
- Low platelets: can cause unusual bleeding or bruising under the skin. Talk to your healthcare provider right away if this happens.
- Low red blood cells: may make you feel tired and you may get tired easily. You may look pale and feel short of breath. Tell your healthcare provider if you have these symptoms.
- Low white blood cells: can cause you to get infections, which may
- Serious infections. People receiving romidepsin for injection can develop serious infections that can sometimes lead to death. These infections can happen during and after treatment with romidepsin for 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: burning with urination
- Fever
- cough
- shortness of breath with or
- without chest pain
- flu-like symptoms muscle aches
- worsening skin problems
- Changes in your heartbeat. Your healthcare provider may check your heart by doing an ECG (electrocardiogram) and blood tests to check your potassium and magnesium levels, before you start romidepsin for injection treatment. 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 for injection. You should drink plenty of fluids in the 3 days after you receive treatment with romidepsin for 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 for injection include:
- nausea, tiredness, vomiting, loss of appetite, changes in sense of taste, constipation, and itching.

These are not all the possible side effects of romidepsin for 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 for

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 for injection. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about Romidepsin for injection that is written for health professionals.

What are the ingredients in romidepsin for injection? Active ingredient: romidepsin

Inactive ingredients: povidone, hydrochloric acid as a pH adjuster. The diluent contains 80% propylene glycol and 20% dehydrated alcohol.

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

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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

he pharmacokinetics of romidepsin was not influenced by age (27 to 83 yrs), gender, race (white vs. black) or mild (estimated creatinine clearance 50 - 80 mL/min), moderate (estimated creatinine clearance 30-50 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 romidepsir

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/m² romidepsin in patients with mild (B1: bilirubin ≤ULN and AST >ULN; B2: bilirubin >ULN but ≤1.5 x ULN and any AST), moderate (bilirubin >1.5 x ULN to ≤3 x ULN and any AST), and severe (bilirubin >3 x ULN and any AST) hepatic impairment were approximately 111%, 96%, and 86% of the corresponding value after administration of 14 mg/n romidepsin in patients with normal (bilirubin ≤upper limit of norma (ULN) and aspartate aminotransferase (AST) ≤ULN) hepatic function respectively. The geometric mean AUC and 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_{inft} as the coefficient of variation (CV) ranged from 30% to

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been performed with romidensing Romidepsin was not mutagenic in vitro in the bacterial reverse mutation assay (Ames test) or the mouse lymphoma assay. Romidepsin togenic 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/m² 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 study romidensin administration resulted in testicular degeneration in rats at 0.33 mg/kg/dose (2 mg/m²/dose) following the clinical dosing schedule. This dose resulted in AUC_{0.82} values that were approximately % the exposure level in patients receiving the recomm of 14 mg/m²/dose. A similar effect was seen in mice after 4 weeks of drug administration at higher doses. Seminal vesicle and pros tate 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/m²/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/m²/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/m²/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/m²/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/m² 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 assess ments, 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

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)		

Table 3. Baseline Patient Characteristics (CTCL Population)

Characteristic	Study 1 (N=96)	Study 2 (N=71)
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)

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

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.		•

REFERENCES

1. OSHA Hazardous Drugs. OSHA. [Accessed on 09/11/2018, from http://www.osha.gov/SLTC/hazardousdrugs/index.html]

HOW SUPPLIED/STORAGE AND HANDLING

epsin for injection is supplied as a kit including a sterile, lyophilized powder in a 10 mg single-dose vial containing 11 mg of romidepsin, 22 mg of the bulking agent, povidone, USP, and hydrochloric acid, NF, as a pH adjuster. In addition, each kit includes a single-dose sterile vial with 2.2 mL deliverable volume of the diluent composed of 80% propylene glycol, USP, and 20% dehydrated alcohol. USP.

Product No.	NDC No.	
704928	63323-926-88	Romidepsin Kit containing 1 vial of romidepsin and 1 vial of diluent for romidepsin per carton.

<u>Storage and Handling</u> Romidepsin for injection is supplied as a kit containing 2 vials in a single carton. The carton must be stored at 20° to 25°C (68° to 77°F) see USP Controlled Room Temperature]

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

The container closure is not made with natural rubber latex. PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient

· Low Blood Counts

Advise patients that treatment with romidepsin 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. 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

omidepsin [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)1.

Nausea and Vomiting
 Advise patients that nausea and vomiting are common following

treatment with romidepsin. Prophylactic antiemetics are recom-mended for all patients. Advise patients to report these symptoms so that appropriate treatment can be instituted [see Adverse Reac-

 Embryo-Fetal Toxicity
 Advise patients that romidepsin can cause fetal harm when administrations and Precautions (5.5) and istered during pregnancy [see Warnings and Precautions (5.5) and Use in Specific Populations (8.1)]. Contraception

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

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

Advise females and males of reproductive potential that romidepsin

may cause infertility [see Nonclinical Toxicology (13.1)]