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

BELEODAQ® (belinostat) for injection, for intravenous use
Initial U.S. Approval: 2014

----------RECENT MAJOR CHANGES----------
Dosage and Administration (2.3, 2.4, 2.6) M/202Y

----------INDICATIONS AND USAGE----------
Beleodaq is a histone deacetylase inhibitor indicated for the treatment of adult patients with relapsed or refractory peripheral T-cell lymphoma (PTCL).

This indication is approved under accelerated approval based on tumor response rate and duration of response. An improvement in survival or disease-related symptoms has not been established. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trial. (1)

----------DOSAGE AND ADMINISTRATION----------
- Recommended dosage of Beleodaq is 1,000 mg/m^2 administered over 30 minutes by intravenous infusion once daily on days 1 through 5 of a 21-day cycle. Cycles can be repeated until disease progression or unacceptable toxicity. (2.1)
- Treatment discontinuation or interruption with or without dosage reductions by 25% may be needed to manage adverse reactions (2.2)
- Reduce dosage in patients with moderate hepatic or renal impairment. (2.3, 2.4, 8.6, 8.7)
- Avoid use in patients with severe hepatic or renal impairment. (2.3, 2.4, 8.6, 8.7)
- Modify dosage in patients known to be homozygous for the UGT1A1*28 allele. (2.5)
- See the full prescribing information for preparation and administration instructions. (2.7)

----------DOSAGE FORMS AND STRENGTHS----------
For injection: 500 mg, lyophilized powder in single-dose vial for reconstitution (3)

----------CONTRAINDICATIONS----------
None. (4)

----------WARNINGS AND PRECAUTIONS----------
- Hematologic Toxicity: Thrombocytopenia, leukopenia (neutropenia and lymphopenia), and anemia: Monitor blood counts and modify dosage for hematologic toxicities. (2.2, 5.1)
- Infection: Serious and fatal infections (e.g., pneumonia and sepsis). (5.2)
- Hepatotoxicity: Beleodaq may cause hepatic toxicity and liver function test abnormalities. Monitor liver function tests and omit or modify dosage for hepatic toxicities. (2.2, 5.3)
- Tumor lysis syndrome: Monitor patients with advanced stage disease and/or high tumor burden and take appropriate precautions (5.4)
- Gastrointestinal Toxicity: Nausea, vomiting, and diarrhea occur with Beleodaq and may require antiemetic and antidiarrheal medications. (5.5)
- Embryo-Fetal Toxicity: Can cause fetal harm. (5.6)

----------ADVERSE REACTIONS----------
The most common adverse reactions (>25%) are nausea, fatigue, pyrexia, anemia, and vomiting. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Acrotech Biopharma Inc at 1-888-292-9617 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

----------DRUG INTERACTIONS----------
UGT1A1 Inhibitors: Avoid use or modify dosage if use is unavoidable. (2.6, 7.1)

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

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

Revised: 11/2024

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Beleodaq is indicated for the treatment of adult patients with relapsed or refractory peripheral T-cell lymphoma (PTCL).

This indication is approved under accelerated approval based on tumor response rate and duration of response *[see Clinical Studies (14)]*. An improvement in survival or disease-related symptoms has not been established. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trial.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dosage of Beleodaq is 1,000 mg/m^2 administered over 30 minutes by intravenous infusion once daily on Days 1 through 5 of a 21-day cycle. Cycles can be repeated every 21 days until disease progression or unacceptable toxicity.

2.2 Dosage Modification for Hematologic and Non-Hematologic Toxicities

Table 1 displays the recommended Beleodaq dosage modifications for hematologic and non-hematologic toxicities. Base dosage adjustments for thrombocytopenia and neutropenia on platelet and absolute neutrophil nadir (lowest value) counts in the preceding cycle of therapy.

- Absolute neutrophil count (ANC) should be greater than or equal to 1 x 10^9/L and the platelet count should be greater than or equal to 50 x 10^9/L prior to the start of each cycle and prior to resuming treatment following toxicity. Resume subsequent treatment with Beleodaq according to the guidelines described in Table 1 below. Discontinue Beleodaq in patients who have recurrent ANC nadirs less than 0.5 x 10^9/L and/or recurrent platelet count nadirs less than 25 x 10^9/L after two dosage reductions.
- Other toxicities must be NCI-CTCAE Grade 2 or less prior to re-treatment.

Monitor complete blood counts at baseline and weekly. Perform serum chemistry tests, including renal and hepatic functions prior to the start of the first dose of each cycle.

Table 1: Dosage Modifications for Hematologic and Non-Hematologic Toxicities

	Dosage Modification
Dosage Modifications due to Hematologic Toxicities	
Platelet count ≥ 25 x 10^9/L and nadir ANC ≥ 0.5 x 10^9/L	No Change
Nadir ANC < 0.5 x 10^9/L (any platelet count)	Decrease dosage by 25% (750 mg/m^2)
Platelet count < 25 x 10^9/L (any nadir ANC)	
Dosage Modifications due to Non-Hematologic Toxicities	
Any CTCAE Grade 3 or 4 adverse reaction[a]	Decrease dosage by 25% (750 mg/m^2)
Recurrence of CTCAE Grade 3 or 4 adverse reaction after two dosage reductions	Discontinue Beleodaq

[a] For nausea, vomiting, and diarrhea, dose modification may not be necessary if the duration is less than 7 days with supportive management

2.3 Recommended Dosage in Patients with Hepatic Impairment

Beleodaq dosage in patients with moderate hepatic impairment (total bilirubin > 1.5 to 3 x ULN, any aspartate aminotransferase (AST)) is 500 mg/m^2 administered over 30 minutes by intravenous infusion once daily on Days 1 through 5 of a 21-day cycle. Avoid use of Beleodaq in patients with severe hepatic impairment (total bilirubin > 3 x ULN, any AST). No dosage adjustment is recommended for patients with mild hepatic

impairment (total bilirubin ≤ 1.5 x ULN, any AST). Hepatic impairment is defined per the National Cancer Institute Organ Dysfunction Working Group.

2.4 Recommended Dosage in Patients with Renal Impairment

Beleodaq dosage in patients with moderate renal impairment (creatine clearance [CLcr] 30 to <60 mL/min) is 500 mg/m^2 administered over 30 minutes by intravenous infusion once daily on Days 1 through 5 of a 21-day cycle. Avoid use of Beleodaq in patients with severe renal impairment (CLcr < 30 mL/min). No dosage adjustment is recommended for patients with mild renal impairment (CLcr 60 to < 90 mL/min).

2.5 Dosage Modification for Patients with Reduced UGT1A1 Activity

Reduce the starting dose of Beleodaq to 750 mg/m^2 in patients known to be homozygous for the UGT1A1*28 allele *[see Clinical Pharmacology (12.5)]*.

2.6 Dosage Modification for Concomitant Use with UGT1A1 Inhibitors

Avoid concomitant use of Beleodaq with UGT1A1 inhibitors. If concomitant use of a UGT1A1 inhibitor is unavoidable, reduce the Beleodaq dosage by 25% as shown in Table 2.

Table 2: Dosage Modifications for Concomitant Use with a UGT1A1 Inhibitor

Beleodaq Starting Dosage	Beleodaq Modified Dosage
1,000 mg/m^2	750 mg/m^2
750 mg/m^2	562.5 mg/m^2
500 mg/m^2	Interrupt Beleodaq treatment for the duration of UGT1A1 inhibitor use. After discontinuation of a UGT1A1 inhibitor of 5 half-lives, resume the Beleodaq dosage that was taken prior to initiating the UGT1A1 inhibitor.

2.7 Preparation and Administration

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

Preparation:

- Aseptically reconstitute each vial of Beleodaq by adding 9 mL of Sterile Water for Injection into the Beleodaq vial with a suitable syringe to achieve a concentration of 50 mg of belinostat per mL. Swirl the contents of the vial until there are no visible particles in the resulting solution. If not used immediately, the reconstituted product may be stored for up to 12 hours at room temperature (15°C to 25°C; 59°F to 77°F).
- Aseptically withdraw the volume needed for the required dosage (based on the 50 mg/mL concentration and the patient's BSA [m^2]) and transfer to an infusion bag containing 250 mL of 0.9 % Sodium Chloride Injection. If not used immediately, the infusion bag with drug solution may be stored at room temperature (15°C to 25°C; 59°F to 77°F) for up to 36 hours including infusion time.
- Visually inspect the solution for particulate matter. Do not use if cloudiness or particulates are observed.

Administration:

- Connect the infusion bag containing drug solution to an infusion set with a 0.22 micron in-line filter for administration.
- Infuse intravenously over 30 minutes. If infusion site pain or other symptoms potentially attributable to the infusion occur, the infusion time may be extended to 45 minutes.

3 DOSAGE FORMS AND STRENGTHS

For injection: 500 mg, lyophilized powder in single-dose vial for reconstitution

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Hematologic Toxicity

Beleodaq can cause thrombocytopenia, leukopenia (neutropenia and lymphopenia), and/or anemia; monitor blood counts weekly during treatment, and modify dosage as necessary *[see Dosage and Administration (2.2)* and *Adverse Reactions (6.1)]*.

5.2 Infections

Serious and sometimes fatal infections, including pneumonia and sepsis, have occurred with Beleodaq. Do not administer Beleodaq to patients with an active infection. Patients with a history of extensive or intensive chemotherapy may be at higher risk of life threatening infections *[see Adverse Reactions (6.1)]*.

5.3 Hepatotoxicity

Beleodaq can cause fatal hepatotoxicity and liver function test abnormalities *[see Adverse Reactions (6.1)]*. Monitor liver function tests before treatment and before the start of each cycle. Interrupt or adjust dosage until recovery, or permanently discontinue Beleodaq based on the severity of the hepatic toxicity *[see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)]*.

5.4 Tumor Lysis Syndrome

Tumor lysis syndrome has occurred in Beleodaq-treated patients in the clinical trial of patients with relapsed or refractory PTCL *[see Clinical Studies (14)]*. Monitor patients with advanced stage disease and/or high tumor burden and take appropriate precautions *[see Adverse Reactions (6.1)]*.

5.5 Gastrointestinal Toxicity

Nausea, vomiting and diarrhea occur with Beleodaq *[see Adverse Reactions (6.1)]* and may require the use of antiemetic and antidiarrheal medications.

5.6 Embryo-Fetal Toxicity

Based on its mechanism of action and findings of genotoxicity, Beleodaq can cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1)* and *Nonclinical Toxicology (13.1)]*. Advise pregnant women of the risk to a fetus. Advise females of reproductive potential to use an effective method of contraception during treatment with Beleodaq and for 6 months after the last dose *[see Use in Specific Populations (8.1, 8.3)]*. Advise males with female partners of reproductive potential to use effective contraception during treatment with Beleodaq and for 3 months after the last dose.

6 ADVERSE REACTIONS

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

- Hematologic Toxicity *[see Warnings and Precautions (5.1)]*
- Infection *[see Warnings and Precautions (5.2)]*
- Hepatotoxicity *[see Warnings and Precautions (5.3)]*
- Tumor Lysis Syndrome *[see Warnings and Precautions (5.4)]*
- Gastrointestinal Toxicity *[see Warnings and Precautions (5.5)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of Beleodaq may not reflect the rates observed in practice.

Adverse Reactions in Patients with Peripheral T-Cell Lymphoma

The safety of Beleodaq was evaluated in 129 patients with relapsed or refractory PTCL in the single arm clinical trial in which patients were administered Beleodaq at a dosage of 1,000 mg/m^2 administered over 30 minutes by IV infusion once daily on Days 1 through 5 of a 21-day cycle *[see Clinical Studies (14)]*. The median duration of treatment was 2 cycles (range 1 – 33 cycles).

The most common adverse reactions observed in the trial of patients with relapsed or refractory PTCL treated with Beleodaq were nausea, fatigue, pyrexia, anemia, and vomiting *[see Clinical Studies (14)]*. Table 3 summarizes the adverse reactions regardless of causality from the trial in patients with relapsed or refractory PTCL.

Table 3: Adverse Reactions Occurring in ≥ 10% of Patients with Relapsed or Refractory PTCL (NCI-CTC Grade 1-4)

Adverse Reactions	Percentage of Patients (%) (N=129)	
	All Grades	Grade 3 or 4
All Adverse Reactions	**97**	**61**
Nausea	42	1
Fatigue	37	5
Pyrexia	35	2
Anemia	32	11
Vomiting	29	1
Constipation	23	1
Diarrhea	23	2
Dyspnea	22	6
Rash	20	1
Peripheral Edema	20	0
Cough	19	0
Thrombocytopenia	16	7
Pruritus	16	3
Chills	16	1
Increased Blood Lactate Dehydrogenase	16	2
Decreased Appetite	15	2
Headache	15	0
Infusion Site Pain	14	0
Hypokalemia	12	4
Prolonged QT	11	4
Abdominal pain	11	1
Hypotension	10	3

Adverse Reactions	Percentage of Patients (%) (N=129)	
	All Grades	Grade 3 or 4
Phlebitis	10	1
Dizziness	10	0

Note: Adverse reactions are listed by order of incidence in the "All Grades" category first, then by incidence in " the Grade 3 or 4" category; Measured by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 3.0

Serious Adverse Reactions

Sixty-one patients (47.3%) experienced serious adverse reactions while taking Beleodaq or within 30 days after their last dose of Beleodaq . The most common serious adverse reactions (> 2%) were pneumonia, pyrexia, infection, anemia, increased creatinine, thrombocytopenia, and multi-organ failure. One treatment-related death associated with hepatic failure was reported in the trial.

One patient with baseline hyperuricemia and bulky disease experienced Grade 4 tumor lysis syndrome during the first cycle of treatment and died due to multi-organ failure. A treatment-related death from ventricular fibrillation was reported in another monotherapy clinical trial with Beleodaq. ECG analysis did not identify QTc prolongation.

Discontinuations due to Adverse Reactions

Twenty-five patients (19.4%) discontinued treatment with Beleodaq due to adverse reactions. The adverse reactions reported most frequently as the reason for discontinuation of treatment included anemia, febrile neutropenia, fatigue, and multi-organ failure.

Dosage Modifications due to Adverse Reactions

In the trial, dosage adjustments due to adverse reactions occurred in 12% of Beleodaq-treated patients.

7 DRUG INTERACTIONS

7.1 UGT1A1 Inhibitors

Avoid concomitant administration of Beleodaq with UGT1A1inhibitors. If concomitant use of a UGT1A1 inhibitor is unavoidable, modify the Beleodaq dose *[see Dosage and Administration (2.6)]*.

Belinostat is primarily metabolized by UGT1A1. Concomitant use with a UGT1A1 inhibitor increases belinostat exposure *[see Clinical Pharmacology (12.3)]*, which may increase the risk of Beleodaq adverse reactions.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action, Beleodaq can cause teratogenicity and/or embryo-fetal lethality because it is genotoxic and targets actively dividing cells *[see Clinical Pharmacology (12.1)* and *Nonclinical Toxicology (13.1)]*. There are no available data on Beleodaq use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. No animal reproduction studies were conducted with Beleodaq. Advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population(s) 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 2-4% and 15-20%, respectively.

8.2 Lactation

Risk Summary

There are no data on the presence of belinostat in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in the breastfed child, advise patients that breastfeeding is not recommended during treatment with Beleodaq, and for 2 weeks after the last dose.

8.3 Females and Males of Reproductive Potential

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

Pregnancy Testing

Pregnancy testing is recommended for females of reproductive potential prior to initiating Beleodaq.

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment with Beleodaq 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 Beleodaq and for 3 months after the last dose *[see Nonclinical Toxicology (13.1)]*.

Infertility

Males
Based on findings from animal studies, Beleodaq may impair male fertility. The reversibility of the effect on fertility is unknown *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

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

8.5 Geriatric Use

In the single-arm trial, 48% of patients (N = 62) were ≥ 65 years of age and 10% of patients (N=13) were ≥ 75 years of age *[see Clinical Studies (14)]*. The median age of the trial population was 63 years. Patients ≥ 65 years of age had a higher response rate to Beleodaq treatment than patients < 65 years of age (36% versus 16%) while no meaningful differences in response rate were observed between patients ≥ 75 years of age and those < 75 years of age. No clinically meaningful differences in serious adverse reactions were observed in patients based on age (< 65 years compared with ≥ 65 years or < 75 years of age compared with ≥ 75 years of age).

8.6 Use in Patients with Hepatic Impairment

No dosage adjustment is recommended for patients with mild hepatic impairment (total bilirubin ≤ 1.5 x ULN, any AST). Reduce the Beleodaq dosage in patients with moderate hepatic impairment (total bilirubin > 1.5 to 3 x ULN, any AST) *[see Dosage and Administration (2.3)]*. Avoid use of Beleodaq in patients with severe hepatic impairment (total bilirubin > 3 x ULN, any AST) *[see Clinical Pharmacology (12.3)]*.

Belinostat is metabolized in the liver, moderate hepatic impairment (total bilirubin > 1.5 to 3 x ULN, any AST) and severe hepatic impairment (total bilirubin > 3 x ULN, any AST) increases belinostat exposure *[see Clinical Pharmacology (12.3)]*, which may increase the risk of Beleodaq adverse reactions.

8.7 Use in Patients with Renal Impairment

No dosage adjustment is recommended for patients with mild renal impairment (CLcr 60 to < 90 mL/min). Reduce the Beleodaq dosage in in patients with moderate renal impairment (CLcr 30 to <60 mL/min) *[see Dosage and Administration (2.4)]*. Avoid use of Beleodaq in patients with severe renal impairment (CLcr < 30 mL/min).

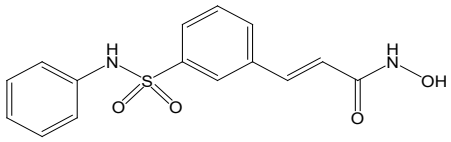
Moderate renal impairment (CLcr 30 to <60 mL/min) increases belinostat exposure *[see Clinical Pharmacology (12.3)]*, which may increase the risk of Beleodaq adverse reactions. The effect of severe renal impairment (CLcr < 30 mL/min) on belinostat pharmacokinetics is unknown *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

No specific information is available on the treatment of overdosage of Beleodaq. There is no antidote for Beleodaq and it is not known if Beleodaq is dialyzable. If an overdose occurs, general supportive measures should be instituted as deemed necessary by the treating physician. The elimination half-life of belinostat is 1.1 hours *[see Clinical Pharmacology (12.3)]*.

11 DESCRIPTION

Beleodaq is a histone deacetylase inhibitor with a sulfonamide-hydroxamide structure. The chemical name of belinostat is (2E)-*N*-hydroxy-3-[3-(phenylsulfamoyl)phenyl]prop-2-enamide. The structural formula is as follows:



The molecular formula is $C_{15}H_{14}N_2O_4S$ and the molecular weight is 318.35 g/mol.

Belinostat is a white to off-white powder. It is slightly soluble in distilled water (0.14 mg/mL) and polyethylene glycol 400 (about 1.5 mg/mL), and is freely soluble in ethanol (> 200 mg/mL). The pKa values are 7.87 and 8.71 by potentiometry and 7.86 and 8.59 by UV.

Beleodaq (belinostat) for injection is supplied as a sterile lyophilized yellow powder containing 500 mg belinostat as the active ingredient. Each vial also contains 1000 mg L-Arginine, USP as an inactive ingredient. The drug product is supplied in a single-dose clear glass vial with a coated stopper and aluminum crimp seal with "flip-off" cap. Beleodaq is intended for intravenous administration after reconstitution with 9 mL Sterile Water for injection, and the reconstituted solution is further diluted with 250 mL of sterile 0.9% Sodium Chloride injection prior to infusion *[see Dosage and Administration (2)]*.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Beleodaq is a histone deacetylase (HDAC) inhibitor. HDACs catalyze the removal of acetyl groups from the lysine residues of histones and some non-histone proteins. *In vitro*, belinostat caused the accumulation of acetylated histones and other proteins, inducing cell cycle arrest and/or apoptosis of some transformed cells. Belinostat shows preferential cytotoxicity towards tumor cells compared to normal cells. Belinostat inhibited the enzymatic activity of histone deacetylases at nanomolar concentrations (<250 nM).

12.2 Pharmacodynamics

Belinostat exposure-response relationships and the time course of pharmacodynamic response are not fully characterized.

Cardiac Electrophysiology

Multiple clinical trials have been conducted with Beleodaq, in many of which ECG data were collected and analyzed by a central laboratory. Analysis of clinical ECG and belinostat plasma concentration data demonstrated no meaningful effect of Beleodaq on cardiac repolarization. None of the trials showed any clinically relevant changes caused by Beleodaq on heart rate, PR duration or QRS duration as measures of autonomic state, atrio-ventricular conduction or depolarization; there were no cases of Torsades de Pointes.

12.3 Pharmacokinetics

The pharmacokinetic characteristics of belinostat were analyzed from pooled data from phase 1/2 clinical studies that used doses of belinostat ranging from 150 to 1200 mg/m^2 (0.15 to 1.2 times the approved recommended dosage).

Distribution

The mean belinostat volume of distribution approaches total body water, indicating that belinostat has limited body tissue distribution. *In vitro* plasma studies have shown that between 92.9% and 95.8% of belinostat is bound to protein in an equilibrium dialysis assay, and was independent of belinostat plasma concentrations from 500 to 25,000 ng/mL.

Elimination

Belinostat elimination half-life is 1.1 hours with a total mean plasma clearance of 1240 mL/min. The total clearance approximates average hepatic blood flow (1500 mL/min), suggesting high hepatic extraction (clearance being flow dependent).

Metabolism

Belinostat is primarily metabolized by hepatic UGT1A1. Belinostat also undergoes hepatic metabolism by CYP2A6, CYP2C9, and CYP3A4 enzymes.

Excretion

Following a single dose of radiolabeled belinostat (100 μCi, 1500 mg) administered as a 30-minute intravenous infusion in patients with recurrent or progressive malignancy, fecal excretion accounted for a mean (± SD) of 9.7% (± 6.5%) of the administered radioactive belinostat dose over 168 hours. The mean (± SD) of the administered radioactive belinostat dose that was excreted in urine over 168 hours was 84.8% (± 9.8%), of which unchanged belinostat accounted for only 1.7%.

Specific Populations

Hepatic Impairment

Belinostat steady state clearance decreased and AUC increased as a function of the degree of liver dysfunction, but were unchanged for C_{max}, half-life and apparent volume of distribution. Mean belinostat clearance was reduced by 18% in mild (total bilirubin ≤ ULN and AST >ULN, or total bilirubin >1 to 1.5 x ULN), 24% in moderate (total bilirubin > 1.5 to 3 times ULN and any value for AST) and 33% in severe hepatic impairment (total bilirubin > 3 to 10 times ULN and any value for AST). Increases in belinostat exposure were correlated with worsening liver function, but there was no obvious relationship between exposure and DLTs during the first cycle of therapy.

Renal Impairment

Belinostat C_{max} increased by 1.7-fold, $AUC_{0-\infty}$ by 1.3-fold and CL_{tot} was unchanged in patients with mild renal impairment (CLcr 60 to <90 ml/min). Belinostat C_{max} and $AUC_{0-\infty}$ increased by 1.7-fold and CL_{tot} decreased by 26% in patients with moderate renal impairment (CLcr 30 < 60 ml/min). The effect of severe renal impairment (CLcr < 30 mL/min) on belinostat pharmacokinetics is unknown.

Drug Interaction Studies

Clinical Studies and Model-Informed Approaches

UGT1A1 inhibitors: Belinostat $t_{1/2}$ increased by 1.5-fold, AUC_{0-inf} increased by 1.4-fold, C_{max} decreased by 33%, and renal excretion increased by 2.5-fold following concomitant administration with atazanavir (UGT1A1 inhibitor), but there was minimal change in steady state clearance. There was minimal change in belinostat glucuronide C_{max}, AUC_{0-24}; however, belinostat glucuronide excretion decreased by 48%.

Warfarin: No clinically significant differences in the pharmacokinetics of R- or S-warfarin were observed when used concomitantly with belinostat.

In Vitro Studies

CYP450 Enzymes: Belinostat and its metabolites are CYP2C8 and CYP2C9 inhibitors.

Transporter Systems: Belinostat is a glycoprotein (P-gp) substrate but is not a P-gp inhibitor.

12.5 Pharmacogenomics

UGT1A1 activity is reduced in individuals with genetic polymorphisms that lead to reduced enzyme activity such as the UGT1A1*28 polymorphism. Approximately 20% of the Black population, 10% of the White population, and 2% of the Asian population are homozygous for the UGT1A1*28 allele. Additional reduced function alleles may be more prevalent in specific populations.

Because belinostat is primarily (80-90%) metabolized by UGT1A1, the clearance of belinostat could be decreased in patients with reduced UGT1A1 activity (e.g., patients with UGT1A1*28 allele). Reduce the starting dose of Beleodaq to 750 mg/m^2 in patients known to be homozygous for the UGT1A1*28 allele to minimize dose limiting toxicities *[see Dosage and Administration (2.5)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been performed with belinostat.

Belinostat was genotoxic in a bacterial reverse mutation test (AMES assay), an in vitro mouse lymphoma cell mutagenesis assay, and an in vivo rat micronucleus assay.

Beleodaq may impair male fertility. Fertility studies using belinostat were not conducted. However, belinostat effects on male reproductive organs observed during the 24-week repeat-dose dog toxicology study included reduced organ weights of the testes/epididymides that correlated with a delay in testicular maturation.

14 CLINICAL STUDIES

Relapsed or Refractory Peripheral T-cell Lymphoma (PTCL)

In an open-label, single-arm, non-randomized international trial conducted at 62 centers, 129 patients with relapsed or refractory PTCL were treated with Beleodaq 1,000 mg/m^2 administered over 30 minutes via IV infusion once daily on Days 1 through 5 of a 21-day cycle. There were 120 patients who had histologically confirmed PTCL by central review evaluable for efficacy. Patients were treated with repeat cycles every three weeks until disease progression or unacceptable toxicity.

Efficacy was evaluated using response rate (complete response and partial response) as assessed by an independent review committee (IRC) using the International Workshop Criteria (IWC) (Cheson 2007). Response assessments were evaluated every 6 weeks for the first 12 months and then every 12 weeks until 2 years from the start of study treatment. Duration of response was measured from the first day of documented response to disease progression or death. Response and progression of disease were evaluated by the IRC using the IWC.

Table 4 summarizes the baseline demographic and disease characteristics of the study population, who were evaluable for efficacy.

Table 4: Baseline Patient Characteristics (PTCL Population)

Characteristics	Evaluable Patients (N=120)
Age (years) Median (range)	64 (29 - 81)
Sex, % Male	52

Characteristics	Evaluable Patients (N=120)
Female	48
Race, %	
White	88
Black	6
Asian	3
Latin	3
Other	2
PTCL Subtype Based on Central Diagnosis, %	
PTCL Unspecified (NOS)	64
Angioimmunoblastic T-cell lymphoma (AITL)	18
ALK-1 negative anaplastic large cell lymphoma (ALCL)	11
Other	7
Baseline Platelet Count, %	
≥100,000/µL	83
<100,000/µL	17
ECOG Performance Status, %	
0	34
1	43
2	22
3	1
Median Time (months) from Initial PTCL Diagnosis (Range)	12 (2.6 - 266.4)
Median Number of Prior Systemic Therapies (Range)	2 (1 - 8)

In all evaluable patients (N = 120) treated with Beleodaq, the overall response rate per central review using IWC was 25.8% (N = 31) (Table 5) with rates of 23.4% for PTCL, NOS and 45.5% for AITL, the two largest subtypes enrolled.

Table 5: Response Analysis per Central Assessment Using IWC in Patients with Relapsed or Refractory PTCL

	Evaluable Patients (N=120)	
Response Rate	**N (%)**	**(95% CI)**
CR+PR	31 (25.8)	18.3 - 34.6
CR	13 (10.8)	5.9 - 17.8
PR	18 (15.0)	9.1 - 22.7

CI=confidence interval, CR=complete response, PR=partial response

The median duration of response based on the first date of response to disease progression or death was 8.4 months (95% CI: 4.5 - 29.4). Of the responders, the median time to response was 5.6 weeks (range 4.3 - 50.4 weeks). Nine patients (7.5%) were able to proceed to a stem cell transplant after treatment with Beleodaq.

15 REFERENCES

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

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

Beleodaq (belinostat) for injection is supplied in single vial cartons; each clear vial contains sterile, lyophilized powder equivalent to 500 mg belinostat.

NDC 72893-002-01**:** Individual carton of Beleodaq single-dose vial containing 500 mg belinostat.

Storage and Handling

Store Beleodaq (belinostat) for injection at room temperature 20°C to 25°C (68°F to 77°F). Excursions are permitted between 15°C and 30°C (59°F and 86°F). Retain in original package until use. [see USP Controlled Room Temperature].

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

17 PATIENT COUNSELING INFORMATION

Physicians should discuss the FDA approved Patient Information Leaflet with patients prior to treatment with Beleodaq. Instruct patients to read the Patient Information Leaflet carefully.

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

Advise patients or their caregivers:

- To report symptoms of nausea, vomiting and diarrhea so that appropriate antiemetic and antidiarrheal medications can be administered *[see Warnings and Precautions (5.5)]*.
- To report any symptoms of thrombocytopenia, leukopenia (neutropenia and lymphopenia), and anemia *[see Warnings and Precautions (5.1)]*.
- To immediately report symptoms of infection (e.g., pyrexia) *[see Warnings and Precautions (5.2)* and *Adverse Reactions (6.1)]*.
- Of the potential risk to the fetus and for women to avoid pregnancy and use effective contraception while receiving Beleodaq and for 6 months after the last dose *[see Warnings and Precautions (5.6)]*. Advise males with female partners of reproductive potential to use effective contraception during treatment with Beleodaq and for 3 months after the last dose.
- To avoid breastfeeding while receiving Beleodaq and for 2 weeks after the last dose *[see Use in Specific Populations (8.2)]*.
- To understand the importance of monitoring liver function test abnormalities and to immediately report potential symptoms of liver injury *[see Dosage and Administration (2.2)* and *Warnings and Precautions (5.3)]*.

Manufactured by:
Cenexi Laboratories Thissen SA
Braine I'Alleud, 1420, Belgium

Manufactured for:
Acrotech Biopharma Inc
East Windsor, NJ 08520 USA

U.S. Patent: 6,888,027

PATIENT INFORMATION
BELEODAQ® (Bē-lēo-dak)
(belinostat) for injection, for intravenous use

Read this Patient Information before you receive treatment with Beleodaq and each time you receive Beleodaq. There may be new information. This leaflet does not take the place of talking to your doctor about your medical condition or your treatment.

What is Beleodaq?

Beleodaq is a prescription medicine used to treat people with a type of cancer called peripheral T-cell Lymphoma (PTCL) that comes back or does not respond to cancer treatment.

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

What should I tell my doctor before receiving Beleodaq?

Before receiving Beleodaq, tell your doctor about all of your medical conditions, including if you:

- have an infection
- have had chemotherapy treatment
- have liver or kidney problems
- have nausea, vomiting, or diarrhea
- are pregnant or plan to become pregnant. Beleodaq can harm your unborn baby. You should not become pregnant while receiving Beleodaq. Tell your doctor right away if you become pregnant while receiving Beleodaq.
- are breastfeeding or plan to breastfeed. It is not known if Beleodaq passes into your breast milk. You and your doctor should decide if you will receive Beleodaq or breastfeed. You should not do both.

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

How will I receive Beleodaq?

- Beleodaq will be given to you by intravenous (IV) injection into your vein, usually over 30 minutes.
- Beleodaq is given one time a day on Days 1 through 5 of a 21-day cycle of treatment.
- You should have regular blood tests before and during your treatment with Beleodaq.
- Your doctor may change your dose of Beleodaq, change when you receive your treatment, or stop treatment if you have certain side effects while receiving Beleodaq.

What are the possible side effects of Beleodaq?

Beleodaq may cause serious side effects, including:

- **Low blood cell counts.** Your doctor will do blood tests to check your blood counts during your treatment with Beleodaq.
  - **Low platelet counts** can cause unusual bleeding or bruising under your skin.
  - **Low red blood cell counts** may make you feel weak, tired, or you get tired easily, you look pale, or you feel short of breath.
  - **Low white blood cell counts** can cause you to get infections, which may be serious.
- **Serious infections.** People receiving Beleodaq may develop serious infections that can sometimes lead to death. You may have a greater risk of life-threatening infections if you have had chemotherapy in the past. Tell your doctor right away if you have any of the following signs or symptoms of an infection: fever, flu-like symptoms, cough, shortness of breath, burning with urination, muscle aches, or worsening skin problems.
- **Liver problems.** Beleodaq may cause liver problems which can lead to death. Your doctor will do blood tests during your treatment with Beleodaq to check for liver problems. Tell your doctor right away if you have any of the following signs or symptoms of liver problems: yellowing of the skin or the white part of your eyes (jaundice), dark urine, itching, or pain in the right upper stomach area.
- **Tumor Lysis Syndrome (TLS).** TLS is caused by a fast breakdown of cancer cells. Your doctor will check you for TLS during treatment with Beleodaq.
- **Nausea, vomiting, and diarrhea** are common with Beleodaq and can sometimes be serious. Tell your doctor if you develop nausea, vomiting or diarrhea. Your doctor may prescribe medicines to help prevent or treat these side effects.

Common side effects of Beleodaq include fatigue, fever, and low red blood cell count.
Tell your doctor if you have any side effect that bothers you or that does not go away.

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

General information about Beleodaq

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

What are the ingredients in Beleodaq?

Active ingredient: belinostat
Inactive ingredients: L-Arginine

Manufactured by: Cenexi Laboratories Thissen SA, Braine l'Alleud, 1420, Belgium
Manufactured for: Acrotech Biopharma Inc, East Windsor, NJ 08520 USA

For more information, go to www.Beleodaq.com or call 1-888-292-9617.

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: 11 2024

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

/s/

NICHOLAS C RICHARDSON
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