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

ZOLINZA™ (vorinostat) Capsules
Initial U.S. Approval: 2006

----------INDICATIONS AND USAGE----------
ZOLINZA is a histone deacetylase (HDAC) inhibitor indicated for:
- Treatment of cutaneous manifestations in patients with cutaneous T-cell lymphoma (CTCL) who have progressive, persistent or recurrent disease on or following two systemic therapies. (1)

---------- DOSAGE AND ADMINISTRATION----------
- 400 mg orally once daily with food. (2.1)
- If patient is intolerant to therapy, the dose may be reduced to 300 mg orally once daily with food. If necessary, the dose may be further reduced to 300 mg once daily with food for 5 consecutive days each week. (2.2, 5)

---------- DOSAGE FORMS AND STRENGTHS ----------
- Capsules: 100 mg (3)

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

----------WARNINGS AND PRECAUTIONS----------
- Pulmonary embolism and deep vein thrombosis have been reported. Monitor patient for pertinent signs and symptoms. (5.1)
- Dose-related thrombocytopenia and anemia have occurred and may require dose modification or discontinuation. (2.2, 5.2, 6)
- Gastrointestinal disturbances (e.g., nausea, vomiting and diarrhea) have been reported. Patients may require antiemetics, antidiarrheals and fluid and electrolyte replacement (to prevent dehydration). (5.3, 6, 17.1)
- Hyperglycemia has been observed. Adjustment of diet and/or therapy for increased glucose may be necessary. (5.4, 5.6)
- QTc prolongation has been observed. Monitor electrolytes and ECGs at baseline and periodically during treatment. (5.5, 5.6)
- Monitor blood cell counts and chemistry tests, including electrolytes, glucose and serum creatinine, every 2 weeks during the first 2 months of therapy and monthly thereafter. (5.6)
- Severe thrombocytopenia and gastrointestinal bleeding have been reported with concomitant use of ZOLINZA and other HDAC inhibitors (e.g., valproic acid). Monitor platelet count. (5.7, 7.2)
- Fetal harm can occur when administered to a pregnant woman. Women should be apprised of the potential harm to the fetus. (5.8)

---------- ADVERSE REACTIONS----------
- The most common adverse reactions (incidence ≥20%) are diarrhea, fatigue, nausea, thrombocytopenia, anorexia and dysgeusia. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Merck & Co., Inc. at 1-877-888-4231 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Coumarin-derivative anticoagulants: Prolongation of prothrombin time and International Normalized Ratio have been observed with concomitant use. Monitor carefully. (7.1)

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

Revised: 10/2006

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ZOLINZA® is indicated for the treatment of cutaneous manifestations in patients with cutaneous T-cell lymphoma who have progressive, persistent or recurrent disease on or following two systemic therapies.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information

The recommended dose is 400 mg orally once daily with food.

Treatment may be continued as long as there is no evidence of progressive disease or unacceptable toxicity.

ZOLINZA capsules should not be opened or crushed *[see How Supplied/Storage and Handling (16)]*.

2.2 Dose Modifications

If a patient is intolerant to therapy, the dose may be reduced to 300 mg orally once daily with food. The dose may be further reduced to 300 mg once daily with food for 5 consecutive days each week, as necessary.

2.3 Dosing in Special Populations

No information is available in patients with renal or hepatic impairment *[see Pharmacokinetics (12.3)]*.

3 DOSAGE FORMS AND STRENGTHS

100 mg white, opaque, hard gelatin capsules with "568" over "100 mg" printed within radial bar in black ink on the capsule body.

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Thromboembolism

As pulmonary embolism and deep vein thrombosis have been reported as adverse reactions, physicians should be alert to the signs and symptoms of these events, particularly in patients with a prior history of thromboembolic events *[see Adverse Reactions (6)]*.

5.2 Hematologic

Treatment with ZOLINZA can cause dose-related thrombocytopenia and anemia. If platelet counts and/or hemoglobin are reduced during treatment with ZOLINZA, the dose should be modified or therapy discontinued. *[See Dosage and Administration (2.2), Warnings and Precautions (5.6) and Adverse Reactions (6).]*

5.3 Gastrointestinal

Gastrointestinal disturbances, including nausea, vomiting and diarrhea, have been reported *[see Adverse Reactions (6)]* and may require the use of antiemetic and antidiarrheal medications. Fluid and electrolytes should be replaced to prevent dehydration *[see Adverse Reactions (6.1)]*. Pre-existing nausea, vomiting, and diarrhea should be adequately controlled before beginning therapy with ZOLINZA.

5.4 Hyperglycemia

Hyperglycemia has been observed in patients receiving ZOLINZA *[see Adverse Reactions (6.1)]*. Serum glucose should be monitored, especially in diabetic or potentially diabetic patients. Adjustment of diet and/or therapy for increased glucose may be necessary.

5.5 QTc Prolongation

A definitive study of the effect of vorinostat on QTc has not been conducted. Three of 86 CTCL patients exposed to 400 mg once daily had Grade 1 (>450-470 msec) or 2 (>470-500 msec or increase of >60 msec above baseline) clinical adverse events of QTc prolongation. In a retrospective analysis of three Phase 1 and two Phase 2 studies, 116 patients had a baseline and at least one follow-up ECG. Four patients had Grade 2 (>470-500 msec or increase of >60 msec above baseline) and 1 patient had

Grade 3 (>500 msec) QTc prolongation. In 49 non-CTCL patients from 3 clinical trials who had complete evaluation of QT interval, 2 had QTc measurements of >500 msec and 1 had a QTc prolongation of >60 msec.

5.6 Monitoring: Laboratory Tests

Careful monitoring of blood cell counts and chemistry tests, including electrolytes, glucose and serum creatinine, should be performed every 2 weeks during the first 2 months of therapy and monthly thereafter. Electrolyte monitoring should include potassium, magnesium and calcium. Baseline and periodic ECGs should be performed during treatment. ZOLINZA should be administered with particular caution in patients with congenital long QT syndrome, and patients taking anti-arrhythmic medicines or other medicinal products that lead to QT prolongation. Hypokalemia or hypomagnesemia should be corrected prior to administration of ZOLINZA, and consideration should be given to monitoring potassium and magnesium in symptomatic patients (e.g., patients with nausea, vomiting, diarrhea, fluid imbalance or cardiac symptoms). *[See Warnings and Precautions (5.5).]*

5.7 Other Histone Deacetylase (HDAC) Inhibitors

Severe thrombocytopenia and gastrointestinal bleeding have been reported with concomitant use of ZOLINZA and other HDAC inhibitors (e.g., valproic acid). Monitor platelet count every 2 weeks during the first 2 months. *[See Drug Interactions (7.2)].*

5.8 Pregnancy

Pregnancy Category D

ZOLINZA can cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies of ZOLINZA in pregnant women. Results of animal studies indicate that vorinostat crosses the placenta and is found in fetal plasma at levels up to 50% of maternal concentrations. Doses up to 50 and 150 mg/kg/day were tested in rats and rabbits, respectively (~0.5 times the human exposure based on $AUC_{0\text{-}24\ hours}$). Treatment-related developmental effects including decreased mean live fetal weights, incomplete ossifications of the skull, thoracic vertebra, sternebra, and skeletal variations (cervical ribs, supernumerary ribs, vertebral count and sacral arch variations) in rats at the highest dose of vorinostat tested. Reductions in mean live fetal weight and an elevated incidence of incomplete ossification of the metacarpals were seen in rabbits dosed at 150 mg/kg/day. The no observed effect levels (NOELs) for these findings were 15 and 50 mg/kg/day (<0.1 times the human exposure based on AUC) in rats and rabbits, respectively. A dose-related increase in the incidence of malformations of the gall bladder was noted in all drug treatment groups in rabbits versus the concurrent control. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

6 ADVERSE REACTIONS

The most common drug-related adverse reactions can be classified into 4 symptom complexes: gastrointestinal symptoms (diarrhea, nausea, anorexia, weight decrease, vomiting, constipation), constitutional symptoms (fatigue, chills), hematologic abnormalities (thrombocytopenia, anemia), and taste disorders (dysgeusia, dry mouth). The most common serious drug-related adverse reactions were pulmonary embolism and anemia.

6.1 Clinical Trials Experience

The safety of ZOLINZA was evaluated in 107 CTCL patients in two single arm clinical studies in which 86 patients received 400 mg once daily.

The data described below reflect exposure to ZOLINZA 400 mg once daily in the 86 patients for a median number of 97.5 days on therapy (range 2 to 480+ days). Seventeen (19.8%) patients were exposed beyond 24 weeks and 8 (9.3%) patients were exposed beyond 1 year. The population of CTCL patients studied was 37 to 83 years of age, 47.7% female, 52.3% male, and 81.4% white, 16.3% black, and 1.2% Asian or multi-racial.

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.

Common Adverse Reactions

Table 1 summarizes the frequency of CTCL patients with specific adverse events, regardless of causality, using the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE, version 3.0).

Table 1
Clinical or Laboratory Adverse Events Occurring in CTCL Patients
(Incidence ≥10% of patients)

	ZOLINZA 400 mg once daily (N=86)			
Adverse Events	**All Grades**		**Grades 3-5***	
	n	**%**	**n**	**%**
Fatigue	45	52.3	3	3.5
Diarrhea	45	52.3	0	0.0
Nausea	35	40.7	3	3.5
Dysgeusia	24	27.9	0	0.0
Thrombocytopenia	22	25.6	5	5.8
Anorexia	21	24.4	2	2.3
Weight Decreased	18	20.9	1	1.2
Muscle Spasms	17	19.8	2	2.3
Alopecia	16	18.6	0	0.0
Dry Mouth	14	16.3	0	0.0
Blood Creatinine Increased	14	16.3	0	0.0
Chills	14	16.3	1	1.2
Vomiting	13	15.1	1	1.2
Constipation	13	15.1	0	0.0
Dizziness	13	15.1	1	1.2
Anemia	12	14.0	2	2.3
Decreased Appetite	12	14.0	1	1.2
Peripheral Edema	11	12.8	0	0.0
Headache	10	11.6	0	0.0
Pruritus	10	11.6	1	1.2
Cough	9	10.5	0	0.0
Upper Respiratory Infection	9	10.5	0	0.0
Pyrexia	9	10.5	1	1.2

* No Grade 5 events were reported.

The frequencies of more severe thrombocytopenia, anemia *[see Warnings and Precautions (5.2)]* and fatigue were increased at doses higher than 400 mg once daily of ZOLINZA.

Serious Adverse Reactions

The most common serious adverse events, regardless of causality, in the 86 CTCL patients in two clinical studies were pulmonary embolism reported in 4.7% (4/86) of patients, squamous cell carcinoma reported in 3.5% (3/86) of patients and anemia reported in 2.3% (2/86) of patients. There were single events of cholecystitis, death (of unknown cause), deep vein thrombosis, enterococcal infection, exfoliative dermatitis, gastrointestinal hemorrhage, infection, lobar pneumonia, myocardial infarction, ischemic stroke, pelvi-ureteric obstruction, sepsis, spinal cord injury, streptococcal bacteremia, syncope, T-cell lymphoma, thrombocytopenia and ureteric obstruction.

Discontinuations

Of the CTCL patients who received the 400-mg once daily dose, 9.3% (8/86) of patients discontinued ZOLINZA due to adverse events. These adverse events, regardless of causality, included anemia, angioneurotic edema, asthenia, chest pain, exfoliative dermatitis, death, deep vein thrombosis, ischemic stroke, lethargy, pulmonary embolism, and spinal cord injury.

Dose Modifications

Of the CTCL patients who received the 400-mg once daily dose, 10.5% (9/86) of patients required a dose modification of ZOLINZA due to adverse events. These adverse events included increased serum creatinine, decreased appetite, hypokalemia, leukopenia, nausea, neutropenia, thrombocytopenia and vomiting. The median time to the first adverse event resulting in dose reduction was 42 days (range 17 to 263 days).

Laboratory Abnormalities

Laboratory abnormalities were reported in all of the 86 CTCL patients who received the 400-mg once-daily dose.

Increased serum glucose was reported as a laboratory abnormality in 69% (59/86) of CTCL patients who received the 400-mg once daily dose; only 4 of these abnormalities were severe (Grade 3). Increased serum glucose was reported as an adverse event in 8.1% (7/86) of CTCL patients who received the 400-mg once daily dose. *[See Warnings and Precautions (5.4).]*

Transient increases in serum creatinine were detected in 46.5% (40/86) of CTCL patients who received the 400-mg once daily dose. Of these laboratory abnormalities, 34 were NCI CTCAE Grade 1, 5 were Grade 2, and 1 was Grade 3.

Proteinuria was detected as a laboratory abnormality (51.4%) in 38 of 74 patients tested. The clinical significance of this finding is unknown.

Dehydration

Based on reports of dehydration as a serious drug-related adverse event in clinical trials, patients were instructed to drink at least 2 L/day of fluids for adequate hydration. *[See Warnings and Precautions (5.3, 5.6).]*

Adverse Reactions in Non-CTCL Patients

The frequencies of individual adverse events were substantially higher in the non-CTCL population. Drug-related serious adverse events reported in the non-CTCL population which were not observed in the CTCL population included single events of blurred vision, asthenia, hyponatremia, tumor hemorrhage, Guillain-Barré syndrome, renal failure, urinary retention, cough, hemoptysis, hypertension, and vasculitis.

7 DRUG INTERACTIONS

7.1 Coumarin-Derivative Anticoagulants

Prolongation of prothrombin time (PT) and International Normalized Ratio (INR) were observed in patients receiving ZOLINZA concomitantly with coumarin-derivative anticoagulants. Physicians should carefully monitor PT and INR in patients concurrently administered ZOLINZA and coumarin derivatives.

7.2 Other HDAC Inhibitors

Severe thrombocytopenia and gastrointestinal bleeding have been reported with concomitant use of ZOLINZA and other HDAC inhibitors (e.g., valproic acid). Monitor platelet count every 2 weeks for the first 2 months. *[See Warnings and Precautions (5.7).]*

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D [See Warnings and Precautions (5.8)]

8.3 Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from ZOLINZA, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

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

8.5 Geriatric Use

Of the total number of patients with CTCL in trials (N=107), 46 percent were 65 years of age and over, while 15 percent were 75 years of age and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Use in Patients with Hepatic Impairment

Vorinostat was not evaluated in patients with hepatic impairment. As vorinostat is predominantly eliminated through metabolism, patients with hepatic impairment should be treated with caution. *[See Clinical Pharmacology (12.3).]*

8.7 Use in Patients with Renal Impairment

Vorinostat was not evaluated in patients with renal impairment. However, renal excretion does not play a role in the elimination of vorinostat. Patients with pre-existing renal impairment should be treated with caution. *[See Clinical Pharmacology (12.3).]*

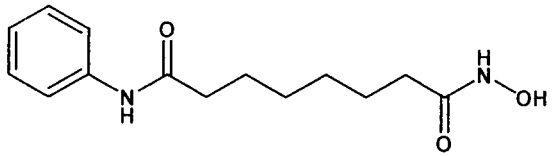
10 OVERDOSAGE

No specific information is available on the treatment of overdosage of ZOLINZA.

In the event of overdose, it is reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive therapy, if required. It is not known if vorinostat is dialyzable.

11 DESCRIPTION

ZOLINZA contains vorinostat, which is described chemically as *N*-hydroxy-*N'*-phenyloctanediamide. The empirical formula is $C_{14}H_{20}N_2O_3$. The molecular weight is 264.32 and the structural formula is:



Vorinostat is a white to light orange powder. It is very slightly soluble in water, slightly soluble in ethanol, isopropanol and acetone, freely soluble in dimethyl sulfoxide and insoluble in methylene chloride. It has no chiral centers and is non-hygroscopic. The differential scanning calorimetry ranged from 161.7 (endotherm) to 163.9°C. The pH of saturated water solutions of vorinostat drug substance was 6.6. The pKa of vorinostat was determined to be 9.2.

Each 100 mg ZOLINZA capsule for oral administration contains 100 mg vorinostat and the following inactive ingredients: microcrystalline cellulose, sodium croscarmellose and magnesium stearate. The capsule shell excipients are titanium dioxide, gelatin and sodium lauryl sulfate.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Vorinostat inhibits the enzymatic activity of histone deacetylases HDAC1, HDAC2 and HDAC3 (Class I) and HDAC6 (Class II) at nanomolar concentrations (IC_{50}<86 nM). These enzymes catalyze the removal of acetyl groups from the lysine residues of proteins, including histones and transcription factors. In some cancer cells, there is an overexpression of HDACs, or an aberrant recruitment of HDACs to oncogenic transcription factors causing hypoacetylation of core nucleosomal histones. Hypoacetylation of histones is associated with a condensed chromatin structure and repression of gene transcription. Inhibition of HDAC activity allows for the accumulation of acetyl groups on the histone lysine residues resulting in an open chromatin structure and transcriptional activation. *In vitro*, vorinostat causes the accumulation of acetylated histones and induces cell cycle arrest and/or apoptosis of some transformed cells. The mechanism of the antineoplastic effect of vorinostat has not been fully characterized.

12.3 Pharmacokinetics

Absorption

The pharmacokinetics of vorinostat were evaluated in 23 patients with relapsed or refractory advanced cancer. After oral administration of a single 400-mg dose of vorinostat with a high-fat meal, the mean ± standard deviation area under the curve (AUC) and peak serum concentration (C_{max}) and the median (range) time to maximum concentration (T_{max}) were 5.5±1.8 μM•hr, 1.2±0.62 μM and 4 (2-10) hours, respectively.

In the fasted state, oral administration of a single 400-mg dose of vorinostat resulted in a mean AUC and C_{max} and median T_{max} of 4.2±1.9 μM•hr and 1.2±0.35 μM and 1.5 (0.5-10) hours, respectively. Therefore, oral administration of vorinostat with a high-fat meal resulted in an increase (33%) in the extent of absorption and a modest decrease in the rate of absorption (T_{max} delayed 2.5 hours) compared to the fasted state. However, these small effects are not expected to be clinically meaningful. In clinical trials of patients with CTCL, vorinostat was taken with food.

At steady state in the fed-state, oral administration of multiple 400-mg doses of vorinostat resulted in a mean AUC and C_{max} and a median T_{max} of 6.0±2.0 μM•hr, 1.2±0.53 μM and 4 (0.5-14) hours, respectively.

Distribution

Vorinostat is approximately 71% bound to human plasma proteins over the range of concentrations of 0.5 to 50 µg/mL.

Metabolism

The major pathways of vorinostat metabolism involve glucuronidation and hydrolysis followed by β-oxidation. Human serum levels of two metabolites, *O*-glucuronide of vorinostat and 4-anilino-4-oxobutanoic acid were measured. Both metabolites are pharmacologically inactive. Compared to vorinostat, the mean steady state serum exposures in humans of the *O*-glucuronide of vorinostat and 4-anilino-4-oxobutanoic acid were 4-fold and 13-fold higher, respectively.

In vitro studies using human liver microsomes indicate negligible biotransformation by cytochromes P450 (CYP).

Excretion

Vorinostat is eliminated predominantly through metabolism with less than 1% of the dose recovered as unchanged drug in urine, indicating that renal excretion does not play a role in the elimination of vorinostat. The mean urinary recovery of two pharmacologically inactive metabolites at steady state was 16±5.8% of vorinostat dose as the *O*-glucuronide of vorinostat, and 36±8.6% of vorinostat dose as 4-anilino-4-oxobutanoic acid. Total urinary recovery of vorinostat and these two metabolites averaged 52±13.3% of vorinostat dose. The mean terminal half-life ($t_{½}$) was ~2.0 hours for both vorinostat and the *O*-glucuronide metabolite, while that of the 4-anilino-4-oxobutanoic acid metabolite was 11 hours.

Special Populations

Based upon an exploratory analysis of limited data, gender, race and age do not appear to have meaningful effects on the pharmacokinetics of vorinostat.

Pediatric

Vorinostat was not evaluated in patients <18 years of age.

Hepatic Insufficiency

Vorinostat was not evaluated in patients with hepatic impairment. *[See Use In Specific Populations (8.6).]*

Renal Insufficiency

Vorinostat was not evaluated in patients with renal impairment. However, renal excretion does not play a role in the elimination of vorinostat. *[See Use In Specific Populations (8.7).]*

Pharmacokinetic effects of vorinostat with other agents

Vorinostat is not an inhibitor of CYP drug metabolizing enzymes in human liver microsomes at steady state C_{max} of the 400 mg dose (C_{max} of 1.2 µM vs IC_{50} of >75 µM). Gene expression studies in human hepatocytes detected some potential for suppression of CYP2C9 and CYP3A4 activities by vorinostat at concentrations higher (≥10 µM) than pharmacologically relevant. Thus, vorinostat is not expected to affect the pharmacokinetics of other agents. As vorinostat is not eliminated via the CYP pathways, it is anticipated that vorinostat will not be subject to drug-drug interactions when co-administered with drugs that are known CYP inhibitors or inducers. However, no formal clinical studies have been conducted to evaluate drug interactions with vorinostat.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been performed with vorinostat.

Vorinostat was mutagenic *in vitro* in the bacterial reverse mutation assays (Ames test), caused chromosomal aberrations *in vitro* in Chinese hamster ovary (CHO) cells and increased the incidence of micro-nucleated erythrocytes when administered to mice (Mouse Micronucleus Assay).

Effects on the female reproductive system were identified in the oral fertility study when females were dosed for 14 days prior to mating through gestational day 7. Doses of 15, 50 and 150 mg/kg/day to rats resulted in approximate exposures of 0.15, 0.36 and 0.70 times the expected clinical exposure based on AUC. Dose dependent increases in corpora lutea were noted at ≥15 mg/kg/day, which resulted in increased peri-implantation losses were noted at ≥50 mg/kg/day. At 150 mg/kg/day, there were increases in the incidences of dead fetuses and in resorptions.

No effects on reproductive performance were observed in male rats dosed (20, 50, 150 mg/kg/day; approximate exposures of 0.15, 0.36 and 0.70 times the expected clinical exposure based on AUC), for 70 days prior to mating with untreated females. *[See Warnings and Precautions (5.8)]*

14 CLINICAL STUDIES

Cutaneous T-cell Lymphoma

In two open-label clinical studies, patients with refractory CTCL have been evaluated to determine their response rate to oral ZOLINZA. One study was a single-arm clinical study and the other assessed several dosing regimens. In both studies, patients were treated until disease progression or intolerable toxicity.

Study 1

In an open-label, single-arm, multicenter non-randomized study, 74 patients with advanced CTCL were treated with ZOLINZA at a dose of 400 mg once daily. The primary endpoint was response rate to oral ZOLINZA in the treatment of skin disease in patients with advanced CTCL (Stage IIB and higher) who had progressive, persistent, or recurrent disease on or following two systemic therapies. Enrolled patients should have received, been intolerant to or not a candidate for bexarotene. Extent of skin disease was quantitatively assessed by investigators using a modified Severity Weighted Assessment Tool (SWAT). The investigator measured the percentage total body surface area (%TBSA) involvement separately for patches, plaques, and tumors within 12 body regions using the patient's palm as a "ruler". The total %TBSA for each lesion type was multiplied by a severity weighting factor (1=patch, 2=plaque and 4=tumor) and summed to derive the SWAT score. Efficacy was measured as either a Complete Clinical Response (CCR) defined as no evidence of disease, or Partial Response (PR) defined as a ≥50% decrease in SWAT skin assessment score compared to baseline. Both CCR and PR had to be maintained for at least 4 weeks.

Secondary efficacy endpoints included response duration, time to progression, and time to objective response.

The population had been exposed to a median of three prior therapies (range 1 to 12).

Table 2 summarizes the demographic and disease characteristics of the Study 1 population.

Table 2
Baseline Patient Characteristics
(All Patients As Treated)

Characteristics	Vorinostat (N=74)
Age (year)	
Mean (SD)	61.2 (11.3)
Median (Range)	60.0 (39.0, 83.0)
Gender, n (%)	
Male	38 (51.4%)
Female	36 (48.6%)
CTCL stage, n (%)	
IB	11 (14.9%)
IIA	2 (2.7%)
IIB	19 (25.7%)
III	22 (29.7%)
IVA	16 (21.6%)
IVB	4 (5.4%)
Racial Origin, n (%)	
Asian	1 (1.4%)
Black	11 (14.9%)
Other	1 (1.4%)
White	61 (82.4%)
Time from Initial CTCL Diagnosis (year)	
Median (Range)	2.6 (0.0, 27.3)
Clinical Characteristics	
Number of prior systemic treatments, median (range)	3.0 (1.0, 12.0)

The overall objective response rate was 29.7% (22/74, 95% CI [19.7 to 41.5%]) in all patients treated with ZOLINZA. In patients with Stage IIB and higher CTCL, the overall objective response rate was 29.5% (18/61). One patient with Stage IIB CTCL achieved a CCR. Median times to response were 55 and 56 days (range 28 to 171 days), respectively in the overall population and in patients with Stage IIB and higher CTCL. However, in rare cases it took up to 6 months for patients to achieve an objective response to ZOLINZA.

The median response duration was not reached since the majority of responses continued at the time of analysis, but was estimated to exceed 6 months for both the overall population and in patients with Stage IIB and higher CTCL. When end of response was defined as a 50% increase in SWAT score from the nadir, the estimated median response duration was 168 days and the median time to tumor progression was 202 days.

Using a 25% increase in SWAT score from the nadir as criterion for tumor progression, the estimated median time-to-progression was 148 days for the overall population and 169 days in the 61 patients with Stage IIB and higher CTCL.

Response to any previous systemic therapy does not appear to be predictive of response to ZOLINZA.

Study 2

In an open-label, non-randomized study, ZOLINZA was evaluated to determine the response rate for patients with CTCL who were refractory or intolerant to at least one treatment. In this study, 33 patients were assigned to one of 3 cohorts: Cohort 1, 400 mg once daily; Cohort 2, 300 mg twice daily 3 days/week; or Cohort 3, 300 mg twice daily for 14 days followed by a 7-day rest (induction). In Cohort 3, if at least a partial response was not observed then patients were dosed with a maintenance regimen of 200 mg twice daily. The primary efficacy endpoint, objective response, was measured by the 7-point Physician's Global Assessment (PGA) scale. The investigator assessed improvement or worsening in overall disease compared to baseline based on overall clinical impression. Index and non-index cutaneous lesions as well as cutaneous tumors, lymph nodes and all other disease manifestations were also assessed and included in the overall clinical impression. CCR required 100% clearing of all findings, and PR required at least 50% improvement in disease findings.

The median age was 67.0 years (range 26.0 to 82.0). Fifty-five percent of patients were male, and 45% of patients were female. Fifteen percent of patients had Stage IA, IB, or IIA CTCL and 85% of patients had Stage IIB, III, IVA, or IVB CTCL. The median number of prior systemic therapies was 4 (range 0.0 to 11.0).

In all patients treated, the objective response was 24.2% (8/33) in the overall population, 25% (7/28) in patients with Stage IIB or higher disease and 36.4% (4/11) in patients with Sezary syndrome. The overall response rates were 30.8%, 9.1% and 33.3% in Cohort 1, Cohort 2 and Cohort 3, respectively. The 300 mg twice daily regimen had higher toxicity with no additional clinical benefit over the 400 mg once daily regimen. No CCR was observed.

Among the 8 patients who responded to study treatment, the median time to response was 83.5 days (range 25 to 153 days). The median response duration was 106 days (range 66 to 136 days). Median time to progression was 211.5 days (range 94 to 255 days).

15 REFERENCES

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2. OSHA Technical Manual, TED 1-0.15A, Section VI: Chapter 2. Controlling Occupational Exposure to Hazardous Drugs. OSHA, 1999. http://www.osha.gov/dts/osta/otm/otm_vi/otm_vi_2.html
3. NIH [2002]. 1999 recommendations for the safe handling of cytotoxic drugs. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, NIH Publication No. 92-2621.
4. American Society of Health-System Pharmacists. (2006) ASHP Guidelines on Handling Hazardous Drugs.
5. Polovich, M., White, J. M., & Kelleher, L.O. (eds.) 2005. Chemotherapy and biotherapy guidelines and recommendations for practice (2nd. ed.) Pittsburgh, PA: Oncology Nursing Society.

16 HOW SUPPLIED/STORAGE AND HANDLING

ZOLINZA capsules, 100 mg, are white, opaque hard gelatin capsules with "568" over "100 mg" printed within the radial bar in black ink on the capsule body. They are supplied as follows:

NDC 0006-0568-40.

Each bottle contains 120 capsules.

Storage and Handling

Store at 20-25°C (68-77°F), excursions permitted between 15-30°C (59-86°F). [See USP Controlled Room Temperature.]

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.[1-5] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

ZOLINZA (vorinostat) capsules should not be opened or crushed. Direct contact of the powder in ZOLINZA capsules with the skin or mucous membranes should be avoided. If such contact occurs, wash thoroughly as outlined in the references. Personnel should avoid exposure to crushed and/or broken capsules *[see Nonclinical Toxicology (13.1)]*.

17 PATIENT COUNSELING INFORMATION

[See FDA-Approved Patient Labeling (17.2)]

17.1 Instructions

Patients should be instructed to drink at least 2 L/day of fluid to prevent dehydration and should promptly report excessive vomiting or diarrhea to their physician. Patients should be instructed about the signs of deep vein thrombosis and should consult their physician should any evidence of deep vein thrombosis develop. Patients receiving ZOLINZA should seek immediate medical attention if unusual bleeding occurs. ZOLINZA capsules should not be opened or crushed.

Patients should be instructed to read the patient insert carefully.

Manufactured for:
MERCK & CO., INC., Whitehouse Station, NJ 08889, USA

Manufactured by:
Patheon, Inc.
Mississauga, Ontario, Canada L5N 7K9

Printed in USA

9762600

U.S. Patent Nos. RE 38,506 E, 6,087,367

17.2 FDA-Approved Patient Labeling

[1]Trademark of MERCK & CO., Inc., Whitehouse Station, New Jersey 08889 USA

TYZEKA™
(telbivudine) Tablets

Rx only

Prescribing Information

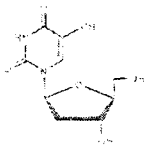
WARNINGS

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination with antiretrovirals.

Severe acute exacerbations of hepatitis B have been reported in patients who have discontinued anti-hepatitis B therapy, including TYZEKA™ (telbivudine). Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue anti-hepatitis B therapy. If appropriate, resumption of anti-hepatitis B therapy may be warranted. (See WARNINGS.)

DESCRIPTION

TYZEKA™ is the trade name for telbivudine, a synthetic thymidine nucleoside analogue with activity against hepatitis B virus (HBV). The chemical name for telbivudine is 1-((2S,4R,5S)-4-hydroxy-5-hydroxymethyltetrahydrofuran-2-yl)-5-methyl-1H-pyrimidine-2,4-dione, or 1-(2-deoxy-β-L-ribofuranosyl)-5-methyluracil. Telbivudine is the unmodified β-L enantiomer of the naturally occurring nucleoside, thymidine. Its molecular formula is $C_{10}H_{14}N_2O_5$, which corresponds to a molecular weight of 242.23. Telbivudine has the following structural formula:



Telbivudine is a white to slightly yellowish powder. Telbivudine is sparingly soluble in water (>20 mg/mL), and very slightly soluble in absolute ethanol (0.7 mg/mL) and n-octanol (0.1 mg/mL).

TYZEKA™ (telbivudine) film-coated tablets are available for oral administration in 600 mg strength. TYZEKA 600 mg film-coated tablets contain the following inactive ingredients: colloidal silicon dioxide, magnesium stearate, microcrystalline cellulose, povidone, and sodium starch glycolate. The tablet coating contains titanium dioxide, polyethylene glycol, talc and hypromellose.

MICROBIOLOGY

Mechanism of Action

Telbivudine is a synthetic thymidine nucleoside analogue with activity against HBV DNA polymerase. It is phosphorylated by cellular kinases to the active triphosphate form, which has an intracellular half-life of 14 hours. Telbivudine 5′-triphosphate inhibits HBV DNA polymerase (reverse transcriptase) by competing with the natural substrate, thymidine 5′-triphosphate. Incorporation of telbivudine 5′-triphosphate into viral DNA causes DNA chain termination, resulting in inhibition of HBV replication. Telbivudine is an inhibitor of both HBV first strand (EC_{50} value = 1.3 ± 1.6 μM) and second strand synthesis (EC_{50} value = 0.2 ± 0.2 μM). Telbivudine 5′-triphosphate at concentrations up to 100 μM did not inhibit human cellular DNA polymerases α, β, or γ. No appreciable mitochondrial toxicity was observed in HepG2 cells treated with telbivudine at concentrations up to 10 μM.

Antiviral Activity

The antiviral activity of telbivudine was assessed in the HBV-expressing human hepatoma cell line 2.2.15, as well as in primary duck hepatocytes infected with duck hepatitis B virus. The concentration of telbivudine that effectively inhibited 50% of viral DNA synthesis (EC_{50}) in both systems was approximately 0.2 μM. The anti-HBV activity of telbivudine was additive with adefovir in cell culture, and was not antagonized by the HIV NRTIs didanosine and stavudine. Telbivudine is not active against HIV-1 (EC_{50} value >100 μM) and was not antagonistic to the anti-HIV activity of abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir, or zidovudine.

Resistance

In an as-treated analysis of the Phase III global registration trial (007 GLOBE study), 59% (252/430) of treatment-naïve HBeAg-positive and 89% (202/227) of treatment-naïve HBeAg-negative patients receiving telbivudine 600 mg once daily achieved nondetectable serum HBV DNA levels (<300 copies/mL) by Week 52.

At Week 52, 145/430 (34%) and 19/227 (8%) of HBeAg-positive and HBeAg-negative telbivudine recipients, respectively, had evaluable HBV DNA (≥1,000 copies/mL). Genotypic analysis detected one or more amino acid substitutions associated with virologic failure (rtM204I, rtL80I/V, rtA181T, rtL180M, rtL229W/V) in 49 of 103 HBeAg-positive and 12 of 12 HBeAg-negative patients with amplifiable HBV DNA and ≥16 weeks of treatment. The rtM204I substitution was the most frequent mutation and was associated with virologic rebound (≥1 $\log_{10}$ increase above nadir) in 34 of 46 patients with this mutation.

Cross-Resistance

Cross-resistance has been observed among HBV nucleoside analogues. In cell-based assays, lamivudine-resistant HBV strains containing either the rtM204I mutation or the rtL180M/rtM204V double mutation had ≥1,000-fold reduced susceptibility to telbivudine. Telbivudine retained wild-type phenotypic activity (1.2-fold reduction) against the lamivudine resistance-associated substitution rtM204V alone. The efficacy of telbivudine against HBV harboring the rtM204V mutation has not been established in clinical trials. HBV encoding the adefovir resistance-associated substitution rtA181V showed 3- to 5-fold reduced susceptibility to telbivudine in cell culture. HBV encoding the adefovir resistance-associated substitution rtN236T remained susceptible to telbivudine.

CLINICAL PHARMACOLOGY

Pharmacokinetics in Adults

The single- and multiple-dose pharmacokinetics of telbivudine were evaluated in healthy subjects and in patients with chronic hepatitis B. Telbivudine pharmacokinetics are similar between both populations.

Absorption and Bioavailability

Following oral administration of telbivudine 600 mg once-daily in healthy subjects (n=12), steady state peak plasma concentration (C_{max}) was 3.69 ± 1.25 μg/mL (mean ± SD) which occurred between 1 and 4 hours (median 2 hours), AUC was 26.1 ± 7.2 μg-h/mL (mean ± SD), and trough plasma concentrations (C_{trough}) were approximately 0.2-0.3 μg/mL. Steady state was achieved after approximately 5 to 7 days of once-daily administration with ~1.5-fold accumulation, suggesting an effective half-life of ~15 hours.

Effects of Food on Oral Absorption

Telbivudine absorption and exposure were unaffected when a single 600-mg dose was administered with a high-fat (~55 g), high-calorie (~950 kcal) meal. TYZEKA™ (telbivudine) may be taken with or without food.

Distribution

In vitro binding of telbivudine to human plasma proteins is low (3.3%). After oral dosing, the estimated apparent volume of distribution is in excess of total body water, suggesting that telbivudine is widely distributed into tissues. Telbivudine was equally partitioned between plasma and blood cells.

Metabolism and Elimination

No metabolites of telbivudine were detected following administration of [^{14}C]-telbivudine in humans. Telbivudine is not a substrate, or inhibitor of the cytochrome P450 (CYP450) enzyme system (see CLINICAL PHARMACOLOGY, Drug Interactions).

After reaching the peak concentration, plasma concentrations of telbivudine declined in a bi-exponential manner with a terminal elimination half-life ($T_{1/2}$) of 40-49 hours. Telbivudine is eliminated primarily by urinary excretion of unchanged drug. The renal clearance of telbivudine approaches normal glomerular filtration rate suggesting that passive diffusion is the main mechanism of excretion. Approximately 42% of the dose is recovered in the urine over 7 days following a single 600 mg oral dose of telbivudine. Because renal excretion is the predominant route of elimination, patients with moderate to severe renal dysfunction and those undergoing hemodialysis require a dose interval adjustment (see DOSAGE AND ADMINISTRATION).

Cardiac Safety

In an *in vitro* hERG model, telbivudine was negative at concentrations up to 10,000 μM. In a thorough QTc prolongation clinical study in healthy subjects, telbivudine had no effect on QT intervals or other electrocardiographic parameters after multiple daily doses up to 1800 mg.

Special Populations

Gender: There are no significant gender-related differences in telbivudine pharmacokinetics.

Race: There are no significant race-related differences in telbivudine pharmacokinetics.

Pediatrics and Geriatrics: Pharmacokinetic studies have not been conducted in children or elderly subjects.

Renal Impairment

Single-dose pharmacokinetics of telbivudine have been evaluated in patients (without chronic hepatitis B) with various degrees of renal impairment (as assessed by creatinine clearance). Based on the results shown in Table 1, adjustment of the dose interval for TYZEKA is recommended in patients with creatinine clearance of <50 mL/min (see DOSAGE AND ADMINISTRATION).

Table 1. Pharmacokinetic Parameters (mean ± SD) of Telbivudine in Subjects with Various Degrees of Renal Function

	Renal Function (Creatinine Clearance in mL/min)				
	Normal (>80) (n=8) 600 mg	Mild (50-80) (n=8) 600 mg	Moderate (30-49) (n=8) 400 mg	Severe (<30) (n=6) 200 mg	ESRD/ Hemodialysis (n=6) 200 mg
C_{max} (μg/mL)	3.4±0.9	3.2±0.9	2.8±1.3	1.6±0.8	2.1±0.9
$AUC_{0\text{-}INF}$ (μg-hr/mL)	28.5±9.6	32.5±10.1	36.0±13.2	32.5±13.2	67.4±36.9
CL_{RENAL} (L/h)	7.6±2.9	5.0±1.2	2.6±1.2	0.7±0.4	

Renally Impaired Patients on Hemodialysis

Hemodialysis (up to 4 hours) reduces systemic telbivudine exposure by approximately 23%. Following dose interval adjustment for creatinine clearance (see DOSAGE AND ADMINISTRATION), no additional dose modification is necessary during routine hemodialysis. TYZEKA should be administered after hemodialysis.

Hepatic Impairment

The pharmacokinetics of telbivudine following a single 600-mg dose have been studied in patients (without chronic hepatitis B) with various degrees of hepatic impairment. There were no changes in telbivudine pharmacokinetics in hepatically impaired subjects compared to unimpaired subjects. Results of these studies indicate that no dosage adjustment is necessary for patients with hepatic impairment.

Drug Interactions

Telbivudine is excreted mainly by passive diffusion so the potential for interactions between telbivudine and other drugs eliminated by renal excretion is low. However, because telbivudine is eliminated primarily by renal excretion, co-administration of telbivudine with drugs that alter renal function may alter plasma concentrations of telbivudine.

Drug-drug interaction studies show that lamivudine, adefovir dipivoxil, cyclosporine and pegylated interferon-alfa 2a do not alter telbivudine pharmacokinetics. In addition, telbivudine does not alter the pharmacokinetics of lamivudine, adefovir dipivoxil, or cyclosporine. No definitive conclusion could be drawn regarding the effects of telbivudine on the pharmacokinetics of pegylated interferon-alfa 2a due to the high inter-individual variability of pegylated interferon-alfa 2a concentrations.

At concentrations up to 12 times that in humans, telbivudine did not inhibit *in vitro* metabolism mediated by any of the following human hepatic microsomal cytochrome P450 (CYP) isoenzymes known to be involved in human medicinal product metabolism: 1A2, 2C9, 2C19, 2D26, 2E1, and 3A4. Based on the above results and the known elimination pathway of telbivudine, the potential for CYP450-mediated interactions involving telbivudine with other medicinal products is low.

INDICATIONS AND USAGE

TYZEKA™ (telbivudine) is indicated for the treatment of chronic hepatitis B in adult patients with evidence of viral replication and either evidence of persistent elevations in serum aminotransferases (ALT or AST) or histologically active disease.

This indication is based on virologic, serologic, biochemical and histologic responses after one year of treatment in nucleoside-treatment-naïve adult patients with HBeAg-positive and HBeAg-negative chronic hepatitis B with compensated liver disease (see Description of Clinical Studies).

Description of Clinical Studies

Adults: The safety and efficacy of telbivudine were evaluated in an international active-controlled, clinical study of 1,367 patients with chronic hepatitis B, called the 007 GLOBE study. All subjects were 16 years of age or older, with chronic hepatitis B, evidence of HBV infection with viral replication (HBsAg-positive, HBeAg-positive or HBeAg-negative, HBV DNA detectable by a PCR assay), and elevated ALT levels ≥1.3 times the upper limit of normal (ULN), and chronic inflammation on liver biopsy compatible with chronic viral hepatitis.

The Week 52 results of the 007 GLOBE study are summarized below.

Clinical Experience in Patients with Compensated Liver Disease: The 007 GLOBE study is a Phase III, randomized, double-blind, multinational study of telbivudine 600 mg PO once daily compared to lamivudine 100 mg once daily for a treatment period of up to 104 weeks in 1,367 nucleoside-naïve chronic hepatitis B HBeAg-positive and HBeAg-negative patients. The primary data analysis was conducted after all subjects had reached Week 52.

HBeAg-positive Subjects: The mean age of subjects was 32 years, 74% were male, 82% were Asian, 12% were Caucasian, and 6% had previously received alfa-interferon therapy. At baseline, subjects had a mean Knodell Necroinflammatory Score ≥7; mean serum HBV DNA as measured by Roche COBAS Amplicor® PCR assay was 9.51 $\log_{10}$ copies/mL; and mean serum ALT was 146 IU/L. Pre- and post-liver biopsy samples were adequate for 86% of subjects.

HBeAg-negative Subjects: The mean age of subjects was 43 years, 77% were male, 65% were Asian, 23% were Caucasian, and 11% had previously received alfa-interferon therapy. At baseline, subjects

concomitant treatment with these or other agents associated with myopathy should weigh carefully the potential benefits and risks and should monitor patients for any signs or symptoms of unexplained