PRODUCT MONOGRAPH

Pr ZOLINZA®

vorinostat capsules

100mg

Histone deacetylase inhibitor, anti-neoplastic agent

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ZOLINZA®

vorinostat capsules

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Non-Medicinal Ingredients
Oral	Capsules 100mg	Gelatin *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

ZOLINZA® is indicated for the treatment of cutaneous manifestations in patients with advanced cutaneous T-cell lymphoma (CTCL) who have progressive, persistent or recurrent disease subsequent to prior systemic therapies.

The indication was approved based on response rate demonstrated in a single-arm phase II study (see CLINICAL TRIALS).

Geriatrics (≥65 years of age):
In clinical studies, the efficacy and safety of ZOLINZA® in the elderly (≥65 years) were comparable to those seen in younger patients (<65 years).

Pediatrics:
The safety and effectiveness of ZOLINZA® in pediatric patients have not been studied.

CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation. For a complete listing, see the Dosage Forms, Composition and Packaging section of the Product Monograph.
- Patients who have severe hepatic impairment (total bilirubin ≥ 3x ULN).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

ZOLINZA® should be administered under the supervision of a physician experienced with the use of chemotherapy and with treatment of cutaneous T-cell lymphoma.

The following are clinically important adverse events:

- Thromboembolism including fatal cases
- Thrombocytopenia and anemia

Cardiovascular

Thromboembolism

Pulmonary embolism and deep vein thrombosis have been reported as drug-related adverse experiences in clinical trials with ZOLINZA®. In the pivotal study in patients with CTCL treated with vorinostat 400 mg once daily (median duration of exposure ~4 months), the reported incidence of pulmonary embolism was 4.7% (4/86) and of deep vein thrombosis was 1.2% (1/86). In all completed and ongoing studies of vorinostat monotherapy in patients with CTCL, the proportion of patients with a venous thromboembolic event was 6.8% (10/147). In greater than 1000 patients with hematologic malignancies and solid tumors who have been treated with vorinostat as monotherapy, or in combination with other chemotherapy agents, in completed and ongoing clinical studies, the proportion of patients that experienced a venous thromboembolic event was approximately 5.0 %. In addition, there was an increase in the incidence of venous thromboembolic events in a randomized, double-blind study of patients with advanced non-small cell lung cancer who received vorinostat (400 mg once daily) in combination with chemotherapy (carboplatin and paclitaxel) as compared to patients who received chemotherapy alone. In this study, deep venous thrombosis and/or pulmonary embolism was reported in 6.5% (8/124) of patients in the vorinostat/chemotherapy treatment arm compared to 2.4% (3/124) of patients in the placebo/chemotherapy treatment arm.

Physicians should closely monitor patients for signs and symptoms of these events, particularly in patients with a prior history of thromboembolic events (see ADVERSE REACTIONS, Serious Adverse Experiences).

QT/QTc Prolongation

ZOLINZA® is associated with QT/QTc interval prolongation (see WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests and ACTION AND CLINICAL PHARMACOLOGY, Cardiac Electrophysiology). Many drugs that cause QT/QTc prolongation are suspected to increase the risk of torsade de pointes.

Torsade de pointes is a polymorphic ventricular tachyarrhythmia. Generally, the risk of torsade de pointes increases with the magnitude of QT/QTc prolongation produced by the drug. Torsade de pointes may be asymptomatic or experienced by the patient as dizziness, palpitations,

syncope, or seizures. If sustained, torsade de pointes can progress to ventricular fibrillation and sudden cardiac death.

Particular care should be exercised when administering ZOLINZA® to patients who are suspected to be at an increased risk of experiencing torsade de pointes during treatment with a QT/QTc-prolonging drug. Risk factors for torsade de pointes in the general population include, but are not limited to, the following: female gender; age 65 years or older; baseline prolongation of the QT/QTc interval; presence of genetic variants affecting cardiac ion channels or regulatory proteins, especially congenital long QT syndromes; family history of sudden cardiac death at <50 years; cardiac disease (e.g., myocardial ischemia or infarction, congestive heart failure, left ventricular hypertrophy, cardiomyopathy, conduction system disease); history of arrhythmias (especially ventricular arrhythmias, atrial fibrillation, or recent conversion from atrial fibrillation); electrolyte disturbances (e.g., hypokalemia, hypomagnesemia, hypocalcemia); bradycardia (<50 beats per minute); acute neurological events (e.g., intracranial or subarachnoid haemorrhage, stroke, intracranial trauma); nutritional deficits (e.g., eating disorders, extreme diets); diabetes mellitus; and autonomic neuropathy.

Physicians who prescribe drugs that prolong the QT/QTc interval should counsel their patients concerning the nature and implications of the ECG changes, underlying diseases and disorders that are considered to represent risk factors, demonstrated and predicted drug-drug interactions, symptoms suggestive of arrhythmia, risk management strategies, and other information relevant to the use of the drug.

Heart Rate

ZOLINZA® has been associated with increases in heart rate (see ACTION AND CLINICAL PHARMACOLOGY, Cardiac Electrophysiology). Increases in heart rate may lead to worsening of cardiac conditions in patients with a history of ischemic heart disease or tachyarrhythmias. Caution should be observed in this patient population.

Drug Interactions

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). Concurrent use of ZOLINZA® with other HDAC inhibitors is not recommended (see DRUG INTERACTIONS, Drug-Drug-Interactions).

Coumarin-Derivative Anticoagulants

Physicians should carefully monitor PT and INR in patients concurrently administered ZOLINZA® and coumarin-derivatives (see DRUG INTERACTIONS, Drug-Drug-Interactions).

Endocrine and Metabolism

Hyperglycemia

Hyperglycemia has been observed commonly in patients receiving ZOLINZA® (see ADVERSE REACTIONS, Laboratory Tests). Serum glucose should be monitored, especially in diabetic or potentially diabetic patients. Adjustment of diet and/or anti-hyperglycemic therapy may be

necessary. Dose reduction or interruption may be considered in patients who develop severe hyperglycemia during ZOLINZA® treatment.

Gastrointestinal

Gastrointestinal disturbances, including nausea, vomiting and diarrhea have been reported very commonly in patients treated with ZOLINZA® (see ADVERSE REACTIONS) which may require the use of antiemetic and antidiarrheal medications. Women may experience more nausea, diarrhea and dysguesia than men.

Dehydration

Dehydration has been reported as a common serious drug-related adverse experience in clinical trials. Fluid and electrolyte replacement should be administered to prevent dehydration (see ADVERSE REACTIONS). Patients should be instructed to drink at least 2 L/day of fluids for adequate hydration. Pre-existing nausea, vomiting, and diarrhea should be adequately controlled before beginning therapy with ZOLINZA®.

Hematologic

Treatment with ZOLINZA® is associated with dose-related thrombocytopenia and anemia. If platelet counts and/or hemoglobin are severely reduced (platelets <25 x 10^3/mm^3 and/or hemoglobin <6.5g/dL) during treatment with ZOLINZA®, the dose should be modified or therapy discontinued (see WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests, ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION).

Peri-Operative Considerations

In some patients recovering from surgery of the bowel and treated peri-operatively with ZOLINZA®, anastomotic healing adverse experiences including fistulas, perforations, and abscess formation have been reported. Therefore, caution should be exercised in the use of ZOLINZA® in the perioperative period when patients require bowel surgery (see ADVERSE REACTIONS, Adverse Experiences in Non-CTCL Patients).

Special Populations

Hepatic impairment

ZOLINZA® was studied in 42 non-CTCL cancer patients with varying degrees of hepatic impairment using single and multiple-dose administration. Although there were no statistically significant differences in any pharmacokinetic parameter across hepatic impairment groups, the degree of hepatic impairment did affect tolerability such that maximum tolerated doses decreased with increasing severity of hepatic impairment. Based on these results, ZOLINZA® should be used with caution at a reduced dose in patients with mild hepatic impairment (total bilirubin >1.0x to 1.5x ULN or total bilirubin ≤ ULN and AST >ULN). ZOLINZA® is not recommended in patients with moderate hepatic impairment (total bilirubin 1.5x - ≤ 3x ULN) as a safe and effective dose has not been established. ZOLINZA® is contraindicated in patients with severe hepatic impairment (total bilirubin >3x ULN). (See CONTRAINDICATIONS, DOSAGE and ADMINISTRATION, Recommended Dose and Dosage Adjustment, Hepatic Impairment, and ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Hepatic Impairment).

Renal impairment
ZOLINZA® has not been studied in patients with renal impairment. Although negligible amount of vorinostat was excreted via the kidney, over 50% of the vorinostat dose was recovered as two major metabolites in the urine (see ACTION AND CLINICAL PHARMACOLOGY). Patients with renal impairment should be treated with caution.

Pregnant Women:
There are no adequate and well-controlled studies in pregnant women using ZOLINZA®. In rats and rabbits administered vorinostat at dosages up to 50 and 150 mg/kg/day, respectively (below the human exposure based on AUC_{0-24}), treatment-related developmental effects including decreased mean live fetal weights, limited sites of incomplete ossifications and limited numbers of skeletal variations at the highest doses of vorinostat tested were observed. An increased incidence of gallbladder malformations was observed in rabbits. The no observed effect level was 15 and 20 mg/kg/day in rats and rabbits, respectively (see TOXICOLOGY, Reproduction).

Women of childbearing potential should be advised to avoid pregnancy while on ZOLINZA®. If ZOLINZA® 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.

Nursing Women:
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®, women should be advised against breast-feeding while taking ZOLINZA®.

Pediatrics:
The safety and effectiveness of ZOLINZA® in pediatric patients have not been studied.

Geriatrics (≥ 65 years of age):
In clinical studies, the safety of ZOLINZA® in the elderly (≥65 years) were comparable to those seen in younger patients (<65 years). No dosage adjustment is necessary in elderly patients.

Monitoring and 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 (see WARNINGS AND PRECAUTIONS, Cardiovascular, QT/QTc prolongation).

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).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

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 most common drug-related adverse experiences in patients on 400 mg once daily could be classified into 4 symptom complexes: gastrointestinal symptoms (diarrhea, nausea, anorexia, weight decreased, vomiting, constipation, decreased appetite), constitutional symptoms (fatigue, chills), hematologic abnormalities (thrombocytopenia, anemia), and taste disorders (dysgeusia, dry mouth).

Clinical Trial Adverse Drug Reactions

Common Clinical Trial Adverse Drug Reactions (≥5%)

Table 1 summarizes the specific drug-related adverse experiences by frequency and National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE, version 3.0) Grade in the CTCL patients who received 400 mg once daily.

Table 1 - Drug-related Clinical or Laboratory Adverse Experiences Occurring in CTCL Patients (Incidence ≥5%)

Adverse Experiences	ZOLINZA® 400 mg once daily (N=86)			
	All Grades		Grade 3-5*	
	n	%	n	%
Fatigue	39	(45.3)	2	(2.3)
Diarrhea	40	(46.5)	0	(0.0)
Nausea	33	(38.4)	3	(3.5)
Dysgeusia	20	(23.3)	0	(0.0)
Thrombocytopenia	22	(25.6)	5	(5.8)
Anorexia	20	(23.3)	2	(2.3)
Weight Decreased	17	(19.8)	1	(1.2)
Dry Mouth	14	(16.3)	0	(0.0)
Vomiting	10	(11.6)	0	(0.0)
Blood Creatinine Increased	11	(12.8)	0	(0.0)
Alopecia	14	(16.3)	0	(0.0)
Decreased Appetite	10	(11.6)	1	(1.2)
Muscle Spasms	14	(16.3)	2	(2.3)
Anemia	11	(12.8)	2	(2.3)
Constipation	9	(10.5)	0	(0.0)
Chills	9	(10.5)	1	(1.2)
Dizziness	6	(7.0)	1	(1.2)
Abdominal Pain	7	(8.1)	1	(1.2)
Proteinuria	7	(8.1)	0	(0.0)
Dyspnea	6	(7.0)	0	(0.0)

Headache	5	(5.8)	0	(0.0)

* None of these adverse experiences were Grade 5.

Serious Drug-Related Adverse Events
The most common serious drug-related adverse experiences in the 86 CTCL patients in two clinical studies receiving 400 mg once daily of ZOLINZA® were pulmonary embolism, reported in 4.7% (4/86) of patients and anemia reported in 2.3% (2/86) of patients. There were single experiences of thrombocytopenia, death (of unknown cause), ischemic stroke, deep vein thrombosis, gastrointestinal hemorrhage, streptococcal bacteremia, dehydration, and syncope.

Three cases (4.1%, 3/74) of squamous cell carcinoma, not considered drug related by the investigator, were reported as serious clinical adverse experiences in the pivotal study,

Dose Modifications and Discontinuations
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 experiences. These adverse experiences included increased serum creatinine, decreased appetite, hypokalemia, leukopenia, nausea, neutropenia, thrombocytopenia and vomiting. The median time to the first adverse experience resulting in dose reduction was 42 days (range 17 to 263 days).

Of the CTCL patients who received the 400-mg once daily dose, 10.5% (9/86) of patients discontinued ZOLINZA® due to drug-related adverse experiences. These adverse experiences included anemia, angioneurotic edema, asthenia, chest pain, death, deep vein thrombosis, ischemic stroke, lethargy, pulmonary embolism and skin lesion.

Dehydration
Based on reports of dehydration as a serious drug-related adverse experience in clinical trials, patients were instructed to drink at least 2 L/day of fluids for adequate hydration. After these precautions were implemented, the incidence of dehydration decreased (see WARNINGS AND PRECAUTIONS, Gastrointestinal and Monitoring and Laboratory Tests).

Abnormal Hematologic and Clinical Chemistry Findings
Laboratory abnormalities were reported in the 86 patients who received the 400-mg dose and one patient who received a 350-mg dose.

Increased serum glucose was detected by laboratory safety tests in 69% (60/87) of CTCL patients, but was severe (Grade 3) in only 5 of these. Hyperglycemia was reported as a drug-related adverse experience in 4.7% (4/86) of CTCL patients who received the 400-mg once daily dose (see WARNINGS AND PRECAUTIONS, Endocrine and Metabolism).

Transient, non-severe increases in serum creatinine were detected in 47.1% (41/87) of CTCL patients.

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

Adverse Experiences in Non-CTCL Patients
In addition to the 107 CTCL patients, 312 patients with malignancies other than CTCL received ZOLINZA® as monotherapy or in combination with other anti-cancer therapies. Drug-related adverse experiences reported in non-CTCL patients were generally similar to those reported in CTCL patients. However, the frequencies of individual adverse experiences were higher in the non-CTCL population. Drug-related serious adverse experiences reported in the non-CTCL population which were not observed in the CTCL population included single experiences of blurred vision, deafness, dysphagia, asthenia, abdominal pain, diverticulitis, hyponatremia, non-small cell lung cancer, tumor hemorrhage, Guillain-Barré syndrome, renal failure, urinary retention, cough, hemoptysis, hypertension and vasculitis.

In some patients recovering from surgery of the bowel and treated peri-operatively with ZOLINZA®, anastomotic healing adverse experiences including fistulas, perforations, and abscess formation have been reported.

DRUG INTERACTIONS

Overview
Clinical studies to evaluate drug-drug interactions of ZOLINZA® have not been conducted. In animal models and *in vitro* human systems, the major pathways of metabolism of vorinostat involve glucuronidation and hydrolysis followed by β-oxidation. It is possible that vorinostat may interact with drugs metabolized via the same pathways.

Drug-Drug Interactions

Table 2- Established or Potential Drug-Drug Interactions

Vorinostat with	Ref	Effect	Clinical comment
Coumarin-Derivative Anticoagulants	CT	Prolongation of prothrombin time (PT) and International Normalized Ratio (INR) were observed infrequently in patients receiving ZOLINZA® concomitantly with coumarin-derivative anticoagulants.	Physicians should carefully monitor PT and INR in patients concurrently administered ZOLINZA® and coumarin derivatives.
Other HDAC Inhibitors	CT	Severe (Grade 4) thrombocytopenia with associated gastrointestinal bleeding and anemia has been reported with the concomitant use of ZOLINZA® and valproic acid.	ZOLINZA® should not be administered concomitantly with other HDAC inhibitors (e.g., valproic acid) as class-specific adverse reactions may be additive.
Other QT/QTc Prolonging Drugs*	T	Concomitant use of ZOLINZA® with another QTc prolonging drug may have an additive effect on QTc interval.	The concomitant use of ZOLINZA® with another QT/QTc-prolonging drug should be avoided to the extent possible.

Drugs that disrupt electrolyte levels**	T	Electrolyte imbalance such as hypokalemia increases risk of QTc interval prolongation	The use of ZOLINZA® with drugs disrupting electrolyte level is discouraged.

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical
*For additional information see Other QT/QTc Prolonging Drugs.
**For additional information see Drugs that Disrupt Electrolyte Levels.

Other QT/QTc Prolonging Drugs: The concomitant use of ZOLINZA® with another QT/QTc-prolonging drug should be avoided to the extent possible. Drugs that have been associated with QT/QTc interval prolongation and/or torsade de pointes include, but are not limited to, the examples in the following list. Chemical/pharmacological classes are listed if some, although not necessarily all, class members have been implicated in QT/QTc prolongation and/or torsade de pointes:

Class IA antiarrhythmics (e.g., quinidine, procainamide, disopyramide); Class III antiarrhythmics (e.g., amiodarone, sotalol, ibutilide); Class 1C antiarrhythmics (e.g., flecainide, propafenone); anthracyclines, including a history of prior treatment (e.g., doxorubicin, epirubicin); tyrosine kinase inhibitors (e.g., sunitinib, nilotinib, lapatinib); antipsychotics (e.g., chlorpromazine, pimozide, haloperidol, droperidol, ziprasidone); antidepressants (e.g., fluoxetine, venlafaxine, tricyclic/tetracyclic antidepressants e.g., amitriptyline, imipramine, maprotiline); opioids (e.g., methadone); macrolide antibiotics and analogues (e.g., erythromycin, clarithromycin, telithromycin); quinolone antibiotics (e.g., moxifloxacin, levofloxacin); pentamidine; antimalarials (e.g., quinine, chloroquine); azole antifungals (e.g., ketoconazole, fluconazole, voriconazole); domperidone; 5-HT_3 receptor antagonists (e.g., dolasetron, ondansetron); tacrolimus; beta-2 adrenoceptor agonists (e.g., salbutamol, formoterol).

Drugs that Disrupt Electrolyte Levels: Drugs that can disrupt electrolyte levels include, but is not limited to, the following: loop, thiazide, and related diuretics; laxatives and enemas; amphotericin B; high dose corticosteroids.

Drug-Food Interactions
Following a single dose 400 mg vorinostat administration, a high-fat meal was associated with a 38% increase in the systemic exposure of vorinostat and a modest decrease in the rate of absorption (2.5 hour delay in median T_{max}). The mean apparent $t_{1/2}$ and C_{max} were similar between the fasted and fed states (see ACTION AND CLINICAL PHARMACOLOGY, Absorption).

Drug-Herb Interactions
Interactions with herbal products have not been established

Drug-Laboratory Interactions
Interactions with laboratory tests have not been established.

Drug-Lifestyle Interactions

Dizziness and syncope have been reported in patients receiving ZOLINZA®, which may affect a patient's ability to drive or operate machinery (see ADVERSE REACTIONS).

DOSAGE AND ADMINISTRATION

Dosing Considerations

- Patients should be instructed to drink at least 2 L/day of fluid to prevent dehydration.
- ZOLINZA® has not been studied in patients <18 years of age.

Recommended Dose and Dosage Adjustment

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

ZOLINZA® should be withheld in the presence of Grade 3-4 drug-related toxicity until the toxicity resolves to Grade 1 or less with the exception of Grade 3 anemia and thrombocytopenia. After recovering from drug-related toxicity, subsequent doses may be reduced to 300 mg orally once daily with food. The dose schedule may be further reduced to 300 mg once daily with food for 5 consecutive days each week, as necessary.

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

Hepatic impairment

ZOLINZA® should be used with caution in patients with mild hepatic impairment (total bilirubin >1.0x to 1.5x ULN or total bilirubin ≤ ULN and AST >ULN). It is recommended to reduce the starting dose to 300 mg orally daily because this is the maximum tolerated dose in this patient population (see ACTION AND CLINICAL PHARMACOLOGY). ZOLINZA® is not recommended in patients with moderate hepatic impairment (total bilirubin 1.5x - ≤ 3x ULN) as a safe and effective dose has not been established. ZOLINZA® is contraindicated in patients with severe hepatic impairment (total bilirubin ≥ 3x ULN) (see WARNINGS AND PRECAUTIONS, Special Populations, Hepatic Impairment).

Renal impairment

ZOLINZA® has not been studied in patients with renal impairment. Caution should be taken when ZOLINZA® is administered in patients with renal impairment (see WARNINGS AND PRECAUTIONS, Special Populations, Renal Impairment, ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions).

Geriatric population

No dosage adjustment is necessary for the elderly (see WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics).

Missed Dose

If a dose is missed, it should be taken as soon as possible. If the patient does not remember until it is nearly time for the next dose, the patient should skip the missed dose and go back to the regular schedule. A double dose of ZOLINZA® should not be taken.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

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

In clinical studies, the frequencies of more severe thrombocytopenia, anemia, fatigue and thromboembolic events were increased at doses higher than 400 mg once daily of ZOLINZA®.

The pharmacological effects may be prolonged after serum levels of active vorinostat are no longer present. It is not known if vorinostat is dialyzable.

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.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

ZOLINZA® is a histone deacetylase (HDAC) inhibitor. HDACs catalyze the removal of acetyl groups from the lysine residues of proteins, including histones and transcription factors.

Vorinostat is a potent inhibitor of histone deacetylases HDAC1, HDAC2 and HDAC3 (Class I) and HDAC6 (Class II) (IC_{50}<86 nM). These enzymes catalyze the removal of acetyl groups from the lysine residues of proteins, including histones. The anti-neoplastic effect of vorinostat is attributed to the inhibition of HDAC activity and subsequent accumulation of acetylated proteins, including histones. Histone acetylation results in transcriptional activation of genes, including tumor suppressor genes, whose expression leads to induction of differentiation, apoptosis and/or inhibition of tumor growth.

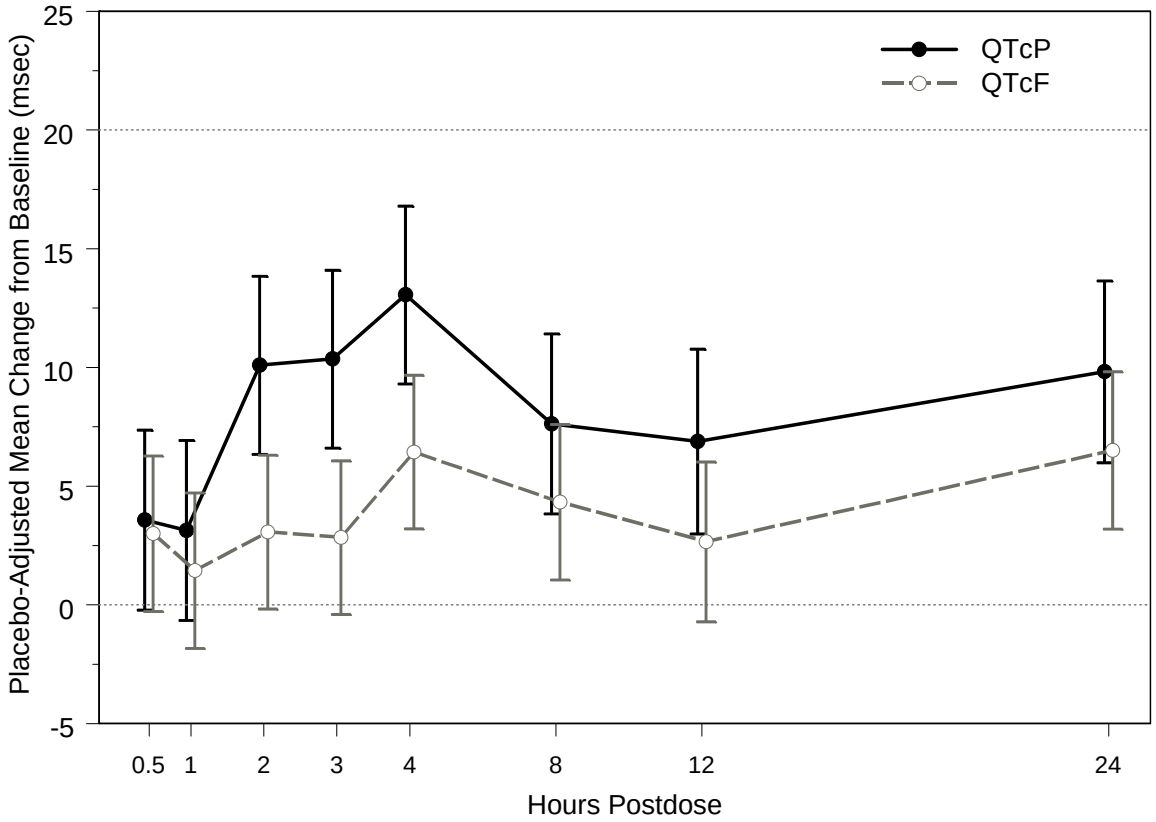
Vorinostat induces apoptosis and inhibits cell growth in a wide variety of transformed cells in culture. In human colon carcinoma cells, inhibition of cell proliferation was observed at concentrations of vorinostat that cause the accumulation of acetylated histones. *In vivo,* vorinostat demonstrates anti-neoplastic activity in rodent tumour models including xenograft models of human prostate, breast and colon carcinoma. Overall, tumour regression was not observed. Rather, vorinostat mediated a decrease in tumour growth rate.

Cardiac Electrophysiology
The effect of ZOLINZA® on cardiac electrophysiology was studied in a placebo-controlled, two period crossover study in which patients with relapsed or refractory cancer (N=24, 12M/12F) were randomised to receive single doses of ZOLINZA® 800 mg and placebo. The QT data were corrected for heart rate using the Fridericia formula (QTcF correction factor 0.33) and a study population-specific correction (QTcP correction factor 0.49). The maximum increase was 13.06ms (90% CI 9.32, 16.81ms) for QTcP at 4 hours post-dosing and 6.51ms (90% CI 3.19, 9.82ms) for QTcF at 24 hours post-dosing.

The magnitude of QTc prolongation observed in a clinical trial will depend on the study conditions, such as the subject population, the dose and duration of treatment, the equipment used, and the methods employed for reading the ECGs and analysing the QTc data. For this reason, QTc data from different clinical trials are not suitable for direct comparison in terms of magnitude of effect.

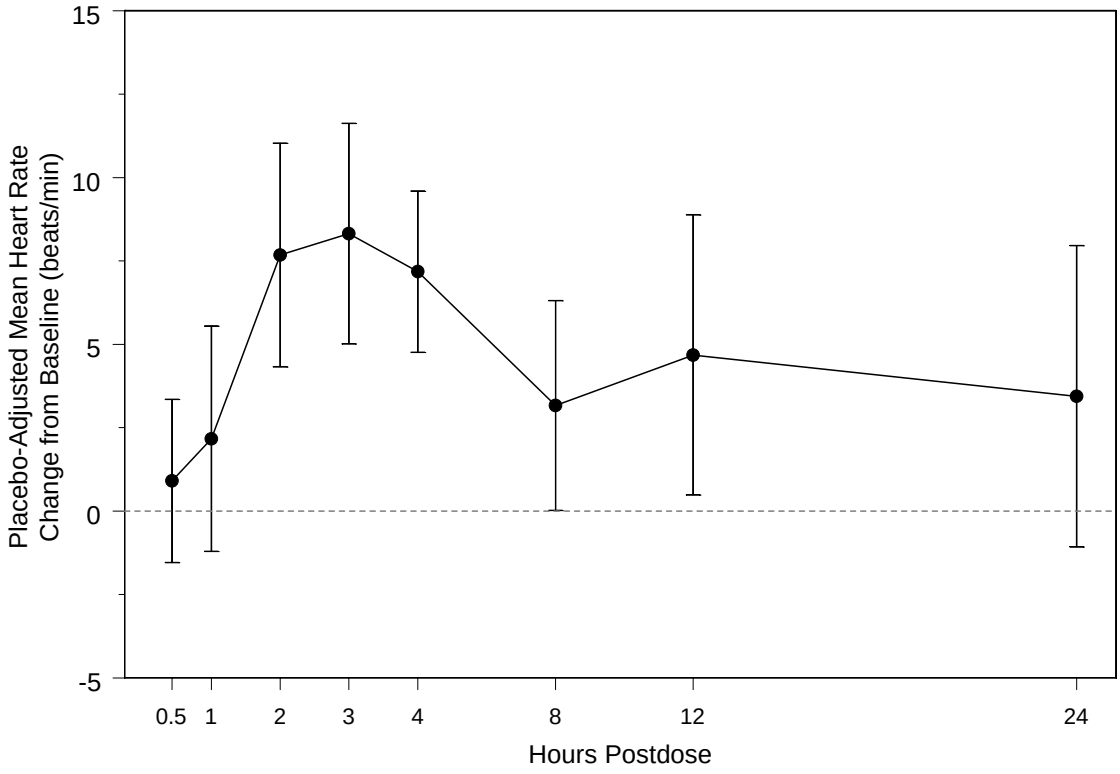
Heart rate increases were observed in the ZOLINZA® 800 mg treatment arm from 2 to 12 hours post-dosing, with a mean maximum increase of 8.32 bpm (90% CI 5.02, 11.63 bpm) at 3 hours post-dosing (see Figure 2).

Figure 1 - Placebo-Adjusted Means and 90% Confidence Intervals for Change-From-Baseline QTc Interval (msec) After Administration of Single-Dose 800-mg Vorinostat to Male and Female Patients with Advanced Cancer (N=24)



QTcP values are corrected for heart rate using a study population-specific correction ($QTc=QT/RR^{0.49}$
QTcP vs RR slope : -0.005, 95% CI -0.022, 0.012
QTcF values are corrected for heart rate using a Fridericia's correction ($QTc=QT/RR^{0.33}$)
QTcF vs. RR slope: 0.074, 95% CI 0.057, 0.091

Figure 2 - Placebo-Adjusted Means and 90% Confidence Intervals for Change-From-Baseline Heart Rate (beats/min) After Administration of Single-Dose 800-mg Vorinostat to Male and Female Patients with Advanced Cancer (N=24)



Pharmacokinetics

The pharmacokinetic parameters of vorinostat following single and multiple doses of 400 mg in patients with cancer are shown in Table 3.

Table 3 - Summary Statistics for Vorinostat Pharmacokinetic Parameters Following Single and Multiple Doses of Vorinostat 400 mg Daily in Male and Female Cancer Patients

Dose/Diet	C_{max} **µM** (Geometric mean [95% CI])	**AUC µM·hr*** (Geometric mean [95% CI])	T_{max} **hr** (Median [range])	$t_{½}$ **hr** (Harmonic mean [jackknife standard deviation])	$f_e^{\|**}$ (Arithmetic mean)
400mg Single Dose Fasted (N=23)	1.12 [0.94, 1.33]	3.87 [3.31, 4.52]	1.5 [0.5, 10]	1.74 [0.78]	0.0021
400mg Single Dose Fed (N=20)	1.02 [0.85, 1.23]	5.33 [4.53, 6.28]	4.0 [2.0, 10]	1.44 [0.65]	0.0030

Dose/Diet	C_{max} **µM** (Geometric mean [95% CI])	**AUC µM·hr*** (Geometric mean [95% CI])	T_{max} **hr** (Median [range])	$t_{½}$ **hr** (Harmonic mean [jackknife standard deviation])	f_e‖** (Arithmetic mean)
400mg Multiple Dose Fed (N=14) 22 Days Once Daily	1.13 [0.91, 1.41]	6.46 [5.42, 7.69]	4.21 [0.5, 14]	1.34 [0.58]	0.0037

* $AUC_{0\text{-}inf}$ reported for single dose data; $AUC_{0\text{-}24\ hr.}$ reported for multiple doses. $AUC_{0\text{-}inf} \sim AUC_{0\text{-}24\ hr}$
‖ Arithmetic mean (single dose fasted N = 22, single dose fed N = 21, multiple dose fed N = 12).
** Fraction excreted unchanged in urine

Absorption: The pharmacokinetics of vorinostat were evaluated in 23 patients with cancer. After oral administration of a single 400-mg dose of vorinostat with a high-fat meal, the mean area under the curve (AUC), peak serum concentration (C_{max}), and the median time to maximum concentration (T_{max}) were approximately 5.33 µM•hr, 1.02 µM and 4.00 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 3.87 µM•hr, 1.12 µM and 1.50 hours, respectively. Oral administration of vorinostat with a high-fat meal resulted in a 38% increase in mean AUC and a modest decrease in the rate of absorption (T_{max} delayed 2.5 hours) compared to the fasted state. Oral administration of multiple 400-mg doses of vorinostat with food resulted in a further 21% increase in mean AUC with C_{max} and T_{max} comparable to those following a single dose in the fed state.

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

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

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

Excretion: Vorinostat is eliminated predominantly through metabolism and vorinostat accounted for less than 1% of the dose recovered as unchanged drug in urine. The mean urinary recovery of two major 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 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.

Drug Interactions with additional pharmacokinetic data
No formal clinical studies have been conducted to evaluate drug interactions with vorinostat. In animal models and *in vitro* human systems, the major pathways of metabolism of vorinostat involve glucuronidation and hydrolysis followed by β-oxidation. It is possible that vorinostat may interact with drugs metabolized via the same pathways.

Vorinostat inhibits CYP drug metabolizing enzymes (CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4) in human liver microsomes only at high concentrations (IC_{50} >75 μM). Using primary human hepatocytes, CYP1A1, 1A2, 2B6, 2C9, 2C19 and 3A4 activities were evaluated. Decreased CYP2C9 and 3A4 activities were observed at concentrations higher (≥10μM) than pharmacologically relevant. Overall, 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.

In vitro studies indicate that vorinostat is not a substrate of human P-glycoprotein (P-gp). In addition, vorinostat has no inhibitory effect on human P-gp-mediated transport of vinblastine (a marker P-gp substrate) at concentrations of up to 100 μM. Thus, vorinostat is not likely to inhibit P-gp at the pharmacologically relevant serum concentration of 2 μM (C_{max}) in humans.

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

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

Geriatrics: 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.

Hepatic Insufficiency: The single dose pharmacokinetics of a 400 mg vorinostat dose administered in a fasted state was evaluated in patients with non-CTCL cancers. There were no statistically significant differences in any pharmacokinetic parameter across hepatic impairment groups. There did not appear to be any trends in any PK parameter with the increasing severity of hepatic impairment.

The safety of multiple daily doses of vorinostat was also evaluated in patients with non-CTCL cancers with varying degrees of hepatic impairment. The highest dose studied in mild, moderate

and severe hepatic impairment was 400, 300 and 200 mg daily, respectively. A total of nine patients had dose-limiting toxicities (DLTs) and the most frequently reported DLT was Grade 4 thrombocytopenia. The DLT event of Grade 4 thrombocytopenia occurred in one (6.7%) patient with mild hepatic impairment at the 400 mg dose and in two (13.3%) patients with moderate hepatic impairment at the 300 mg dose. In patients with severe hepatic impairment, this DLT event occurred in three (27.3%) patients.

Renal Insufficiency: Vorinostat was not evaluated in patients with renal impairment. Vorinostat is eliminated predominantly through metabolism with less than 1% of the dose recovered as unchanged drug in urine. Total recovery of the two major pharmacologically inactive metabolites in the urine, however, averaged approximately 52% of the oral dose.

STORAGE AND STABILITY

Store at room temperature (15 ^{o}C – 30 ^{o}C).

SPECIAL HANDLING INSTRUCTIONS

Direct contact of the powder in ZOLINZA® capsules with the skin or mucous membranes should be avoided. If such contact occurs, wash thoroughly. ZOLINZA® capsules should not be opened or crushed (see TOXICOLOGY).

DOSAGE FORMS, COMPOSITION AND PACKAGING

Each 100 mg ZOLINZA® capsule for oral administration contains 100 mg vorinostat.

Non-medicinal ingredients: magnesium stearate, microcrystalline cellulose and sodium croscarmellose. The capsule shell excipients are gelatin, titanium dioxide and may contain sodium lauryl sulfate.

ZOLINZA®, 100mg capsule, is white, opaque, hard gelatin capsule with "568" over "100 mg" printed within radial bar in black ink on the capsule body. Available in high density polyethylene bottles of 120 capsules.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

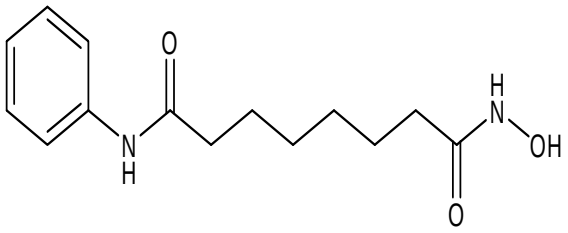
Common name: vorinostat

Chemical name: *N*-hydroxy-*N′*-phenyloctanediamide

Molecular formula: $C_{14}H_{20}N_2O_3$

Molecular mass: 264.32

Structural formula:



Physicochemical properties:

Vorinostat is a white to off-white 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.

CLINICAL TRIALS

Study design

In an open-label, single-arm, multicenter Phase IIb study, 74 patients with CTCL of all stages were treated with 400 mg once daily ZOLINZA®. Dose modification (300 mg once daily for 7days/week, 300 mg for 5 consecutive days/week) was allowed by the protocol after recovery from dose-related toxicities. The primary endpoint was response rate measured by modified Severity Weighted Assessment Tool (mSWAT) in patients with advanced CTCL (Stage IIB and higher) who have progressive, persistent, or recurrent disease on or following at least two systemic therapies. One of these therapies must have contained bexarotene unless the patient was intolerant of or not a candidate for bexarotene therapy.

Extent of skin disease was quantitatively assessed by investigators using mSWAT. 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 mSWAT score.

Efficacy was measured as either a Complete Clinical Response (CCR) defined as no evidence of skin disease, or Partial Response (PR) defined as a ≥50% decrease in skin mSWAT assessment score compared to baseline. Response had to be maintained for at least 4 weeks to be considered either CCR or PR. For patients with Sézary syndrome who have achieved a CCR or PR, peripheral blood flow cytometry was conducted to monitor malignant T cell (CD4+CD26-) counts. However, the presence or worsening of T cell (CD4+CD26-) count in peripheral blood did not overrule a CCR or PR in cutaneous response.

Secondary endpoints included relief of pruritus; response duration; time to objective response; and safety and tolerability. Duration of response was measured from the time when criteria were first met for CCR or PR (whichever was first recorded) until the first date when an increase in skin assessment by mSWAT score was greater than 50% of the difference between baseline score and nadir score.

Study results

Baseline patient demographic and clinical characteristics are shown in Table 4.

Table 4 - Baseline Patient Demographic and Clinical 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	
Presence of clinically abnormal lymph nodes, n (%)	34 (45.9%)
Presence of histologically involved lymph nodes, n (%)	19 (25.7%)
Presence of skin tumor, n (%)	22 (29.7%)
Presence of Sézary syndrome, n (%)	30 (40.5%)
Number of prior systemic treatments, median (range)	3.0 (1.0, 12.0)
BSA involvement (%), median (range)	
Patch	15.6 (0.0, 100.0)
Plaque	5.9 (0.0, 98.0)
Tumor	0.0 (0.0, 91.5)

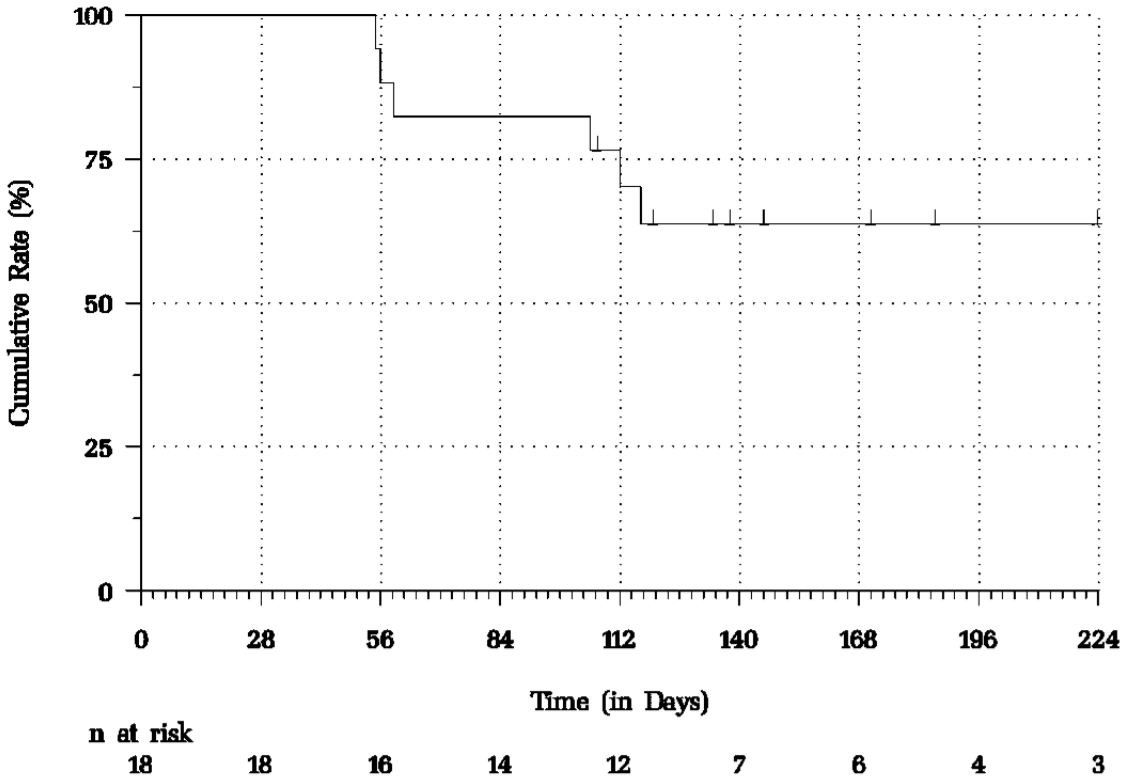
The overall objective response was 29.7% (22/74, see Table 5) in all patients treated with ZOLINZA®. In patients with Stage IIB and higher CTCL, the overall objective response was 29.5% (18/61). One patient with T3 tumor disease and limited skin involvement (1.65% of total body surface area) achieved a CCR. Median time to response was 55 and 56 days (range 28 to 171 days), in the overall population and in patients with Stage IIB and higher, respectively CTCL. Overall, the median time to response was less than 2 months; however, in rare cases it took up to 6 months for patients to achieve an objective response to ZOLINZA®.

The median number of days on ZOLINZA® treatment in this study was 119 days with a range of 2 to 365 days. The median response duration in the 18 responders with stage IIB and higher CTCL was not reached during this study (see Figure 3).

Table 5 - Number of Patients Treated with ZOLINZA® with an Objective Response of Cutaneous Manifestations (All CTCL Patients)

Population		Patients Treated with ZOLINZA® with an Objective Response		
	N	n (%)	(95% CI)	Time to Objective Response† (days) Median (Range)
All Patients	74	22 (29.7%)	(19.7, 41.5)	55 (28, 171)
Stage IIB or Higher‡	61	18 (29.5%)	(18.5, 42.6)	56 (28, 171)
Patients with Sézary syndrome	30	10 (33.3%)	(17.3, 52.8)	56 (28, 171)
Patients with T3 tumor disease	22	5 (22.7%)	(7.8, 45.4)	31 (29, 87)
† Objective Response: confirmed complete clinical response or partial response of cutaneous manifestation				
‡ Stages IIB, III, IVA and IVB				
CI = Confidence Interval				

Figure 3 - Response Duration - Observed Kaplan-Meier Curve during Treatment with Vorinostat For Patients Who Achieved An Objective Response (Patients With Stage IIB And Higher Cancer)



Anti-pruritus and other medications to ameliorate pruritus were allowed during the study. In all CTCL patients treated with ZOLINZA® with pruritus intensity ≥ 3 of 10 points at baseline, 32.3% (21/65) had pruritus relief, as measured by a minimum decrease of 3 points, and 9.2% (6/65) had complete resolution of their pruritus. Similarly, in patients with Stage IIB and higher CTCL, 30.2% (16/53) had pruritus relief, and 11.3% (6/53) had complete resolution of their pruritus. This relief was maintained for at least 4 weeks without an increase in their pruritus medication. Among 23 CTCL patients with pruritus relief, 10 also experienced an objective response while 13 patients experienced pruritus relief without an objective response.

DETAILED PHARMACOLOGY

After oral administration of a single 400-mg dose of vorinostat with a high-fat meal, the mean area under the curve (AUC), peak serum concentration (C_{max}), and the median time to maximum concentration (T_{max}) were approximately 5.33 μM•hr, 1.02 μM and 4.00 hours, respectively. Oral administration of vorinostat with a high-fat meal resulted in a 38% increase in mean AUC and a modest decrease in the rate of absorption (T_{max} delayed 2.5 hours) compared to the fasted 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 6.46 μM•hr, 1.13 μM and 4.21 hours, respectively.

Vorinostat is approximately 71% bound to human plasma proteins over the concentration range of 0.5 to 50 μg/mL. Vorinostat rapidly crossed the placenta in both the rat and rabbit and reached transplacental equilibrium within 30 minutes post-dose.

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

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 major pharmacologically inactive metabolites at steady state was 16±5.8% of the vorinostat dose as the *O*-glucuronide of vorinostat, and 36±8.6% of the vorinostat dose as 4-anilino-4-oxobutanoic acid. Total urinary recovery of these two metabolites averaged 52±13.3% of the 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.

Based upon an exploratory analysis of limited data, gender, race, and age do not appear to have meaningful effects on the pharmacokinetics of vorinostat. Vorinostat was not evaluated in patients <18 years of age or patients with renal impairment.

TOXICOLOGY

Acute Toxicity

Mortality did not occur in either mice or rats following a single oral dose of vorinostat at 2000 mg/kg (only dose tested), which is equivalent to 6,000 mg/m^2 in mice and 12,000 mg/m^2 in rats, and is greater than 24 times the recommended daily human dose on a mg/m^2 basis.

Single-dose studies were also conducted in mice, rats and dogs by the IV route. Mortality was not observed in rats at doses that are equivalent to the recommended daily human dose on a mg/m^2 basis. In mice, the estimated LD_{10} = 1534 mg/kg (4626 mg/m^2). In dogs the lethal dose was > 200 mg/kg (4000 mg/m^2) following 4 hours of continuous infusion and < 72 mg/kg (1440 mg/m^2) following 120 hours of continuous infusion. All doses are greater than the recommended daily human dose on a mg/m^2 basis.

Chronic Toxicity

Vorinostat was evaluated in a series of repeat dose oral toxicology studies of up to 26 weeks in rats at doses of 20, 50 and 150mg/kg/day and in dogs at doses of 20, 60 and 160 mg/kg/day. All doses were < 1 times the human exposure based on AUC_{0-24}.The primary effects observed were

anorexia, decreased food consumption, weight loss, decreased activity, hematologic and gastrointestinal effects.

In rats, a no effect level was not established (< 20 mg/kg/day). From this dose, decreased platelet, WBC and lymphocyte counts were observed. Immunophenotyping indicated that total T lymphocytes, T_H cells, T_c cells, and total B cells were decreased. At the microscopic level erythroid hyperplasia and myeloid hypoplasia was observed in femur and sternum bone marrow. From 50 mg/kg/day, dose-dependent reductions in food consumption, body weight gain, decreased serum globulin, and increased pro-thrombin time was observed. At 150 mg/kg/day, extravascular hemolysis, increased absolute reticulocyte counts and lymphoid depletion (spleen, thymus) were noted.

In a 4-week dog study, a dose of 100 mg/kg/day (high-dose) produced severe adverse clinical signs, decreased body weight and food consumption, hematological toxicity and gastrointestinal lesions. These animals were terminated after 17 days of dosing. The no effect level was 40 mg/kg/day (mid-dose). In the 26-week dog study gastrointestinal lesions were also noted along the length of the GI tract at 160 mg/kg/day (no effect level = 60 mg/kg/day).

Reversibility of toxic effects was assessed in the high-dose rats and dogs. Most findings were reversible. Partial recovery was observed with respect to body weight (male rats) and select erythroid and myeloid blood cell parameters (male rats). In dogs, recovery was observed for all GI findings in the 26-week but not 4-week study.

Carcinogenicity
Carcinogenicity studies have not been performed with vorinostat.

Genotoxicity
Vorinostat was assessed with respect to mutagenicity and clastogenicity in the *in vitro* bacterial reverse mutation assay (Ames test), chromosome aberration test using Chinese Hamster Ovary (CHO) cells and human peripheral blood lymphocytes, and the *in vivo* chromosomal aberration test using mouse bone marrow cells.

In the bacterial reverse mutation assays (Ames test), vorinostat was weakly positive in *S. typhimurium* at the highest concentration tested.

Vorinostat was clastogenic in the chromosomal aberration test when tested with CHO cells (transformed cells) but not with normal human peripheral blood lymphocytes (non-transformed cells). Chromosomal aberrations in CHO cells were associated with suppression of cell growth, suggesting that aberration induction may be an indirect effect due to perturbation of DNA synthesis.

In the *in vivo* mouse micronucleus assay male mice were orally dosed with vorinostat at 500, 1000 and 2000 mg/kg. Vorinostat was weakly positive at doses ≥500 mg/kg.

Reproduction

Female rats were orally dosed with vorinostat at 15, 50 and 150 mg/kg/day. Female toxicity was observed at 150 mg/kg/day. There were no vorinostat-related effects on mating, fertility or fecundity indices at doses up to 150 mg/kg/day (<1 times the human exposure based on AUC_{0-24}). An increased number of corpora lutea was observed from 15 mg/kg/day. An increased number of resorptions and increased percent peri-implantation loss was observed from 50 mg/kg/day. An increase in percent post-implantation loss and a decreased number of live fetuses per litter were observed at 150 mg/kg/day. The no observed effect level for reproductive performance, based on the number of corpora lutea, was < 15 mg/kg/day (<1 times the human exposure based on AUC_{0-24}).

Male rats were orally dosed with vorinostat at 20, 50 and 150 mg/kg/day. There were no treatment-related effects of vorinostat on mating performance, fertility, embryonic/fetal survival, sperm count and motility, testicular weight or testicular and epididymal histomorphology and, when mated with untreated females, there were no effects on embryonic/fetal survival up to 150 mg/kg/day (<1 times the human exposure based on AUC_{0-24}).

Development
Rats and rabbits were orally administered vorinostat at 5, 15 and 50 mg/kg/day and 20, 50 and 150 mg/kg/day, respectively. Treatment-related developmental effects including decreased mean live fetal weights, low incidences of incomplete ossifications and low incidences of skeletal variations at the highest doses of vorinostat tested were observed. An increased incidence of gallbladder malformations was observed in rabbits. The no observed effect level was 15 and 20 mg/kg/day in rats and rabbits, respectively (<1 times the human exposure based on AUC_{0-24}).

Placental transfer
Vorinostat rapidly crossed the placenta in rats and rabbits at doses that are equivalent to less than 1 times human exposure (based on AUC_{0-24}). Transplacental equilibrium was reached within 30 minutes post-dose.

SAFETY PHARMACOLOGY
Vorinostat did not inhibit hERG potassium currents in stably transfected Chinese Hamster Ovary cells (N=7-9/concentration) at nominal concentrations up to 300 μM (limit of solubility). No QTc prolongation was observed in a cardiovascular telemetry study in conscious dogs (N=4) receiving single oral doses of 20, 60, or 160 mg/kg vorinostat according to an escalating dose design. Treatment-related increases in heart rate were observed at 60 and 160 mg/kg vorinostat.

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PART III: CONSUMER INFORMATION

Pr ZOLINZA®
vorinostat capsules

This leaflet is part III of a three-part "Product Monograph" published when ZOLINZA® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about ZOLINZA®. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
ZOLINZA® is used for the treatment of a type of cancer called cutaneous T-cell lymphoma in patients who have progressive, persistent, or recurrent disease after previous systemic therapies. It is also called CTCL.

What is Cutaneous T-cell lymphoma:
Cutaneous T-cell lymphoma (CTCL) is a disease in which certain cells of the lymph system develop into cancer cells and affect your skin. The cells are called T-cells. They are the white blood cells which help to fight infection. CTCL usually develops slowly. Patches can first form on the skin and may develop into tumors in the skin. The cancer can continue to spread to large areas of the skin and to other organs of the body.

What it does:
ZOLINZA® is a new type of anti-cancer medicine known as an HDAC inhibitor. The full name for HDAC is histone deacetylase. ZOLINZA® has been shown to slow or stop the growth of cancer cells. It has also been shown to cause the death of cancer cells.

When it should not be used:
Do not take ZOLINZA® if you:
- are allergic to any of the ingredients in ZOLINZA®
- have severe liver disease

What the medicinal ingredient is:
vorinostat

What the non-medicinal ingredients are:
magnesium stearate, microcrystalline cellulose and sodium croscarmellose. The capsule shell excipients are gelatin, titanium dioxide and may contain sodium lauryl sulfate.

What dosage forms it comes in:
Capsules: 100mg vorinostat

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

ZOLINZA® should be prescribed and managed by a doctor experienced with the use of cancer drugs and with treatment of cutaneous T-cell lymphoma.

The following are serious side effects:
- blood clots (venous thromboembolism), cases of death have been reported
- reduced red blood cells (anemia) and platelets (thrombocytopenia)

BEFORE you use ZOLINZA® talk to your doctor or pharmacist if you:
- have any medical problems
- have diabetes, especially with associated nerve disorders
- have any allergies
- have had a blood clot in your lung (pulmonary embolus)
- have had a blood clot in a vein (a blood vessel) anywhere in your body (deep vein thrombosis)
- are pregnant or planning to become pregnant. ZOLINZA® may harm your unborn baby
- are breast-feeding or plan to breast-feed. It is not known if ZOLINZA® passes into breast milk. You should stop breast-feeding once you start treatment with ZOLINZA®
- have liver disease
- have QT/QTc prolongation or a family history of QT/QTc prolongation
- have heart disease
- have a personal history of fainting spells
- have a family history of sudden cardiac death at <50 years
- have electrolyte disturbances (e.g., low blood potassium or magnesium levels) or conditions that could lead to electrolyte disturbances (e.g., vomiting, diarrhea, dehydration)
- have an eating disorder or are following a strict diet
- have had recent bowel surgery or plan on having bowel surgery

ZOLINZA® has not been studied in children under 18 years of age.

ZOLINZA® may have an effect on the electrical activity of the heart known as QT/QTc prolongation. This effect can be measured as a change in the electrocardiogram (ECG). In very rare cases, drugs with this effect on the ECG can lead to disturbances in heart rhythm (arrhythmias/dysrhythmias) that could result in dizziness, palpitations (sensation of rapid,

pounding, or irregular heart beat), fainting or death. These heart rhythm disturbances are more likely in patients with risk factors, such as heart disease, or in the presence of certain interacting drugs. In general, females and people more than 65 years in age are at higher risk. It is important to follow the instructions of your doctor with regard to dosing or any special tests. If you experience any symptoms of a possible heart rhythm disturbance, such as dizziness, palpitations (sensation of rapid, pounding, or irregular heart beat), fainting, or seizures, you should seek immediate medical attention.

Electrocardiograms (ECGs) may be required periodically to monitor the risk of potentially serious side effects during treatment with ZOLINZA®.

Dizziness and fainting have been reported in patients receiving ZOLINZA®, which may affect your ability to drive or operate machinery.

INTERACTIONS WITH THIS MEDICATION

Tell your doctor or pharmacist all the medicines you are taking or planning to take, including medicines you can buy without prescription, vitamins, herbal and alternative products, especially the following medicines:

- other histone deacetylase (HDAC) inhibitors (e.g. valproic acid, divalproex, medicines used to treat seizures and mood disorders). Other HDAC inhibitors should not be taken with ZOLINZA®
- warfarin (Coumadin®) or any other blood thinner. Frequent blood tests may be required while you are taking ZOLINZA®
- drugs to treat heart rhythm disturbances
- painkillers
- antipsychotics
- antidepressants
- drugs used to treat infections (e.g., antibiotics and antifungals)
- drugs to prevent or treat nausea and vomiting
- drugs for asthma
- diuretics
- other cancer drugs.

This list includes some, but not all, of the drugs that may increase the risk of heart rhythm problems and other side effects while receiving ZOLINZA®. You should check with your doctor or pharmacist before taking any other medication with ZOLINZA®.

PROPER USE OF THIS MEDICATION

If ZOLINZA® capsules are broken or crushed, do not touch the capsules or the contents of the capsules. If the contents of a broken capsule get on the skin or in the eyes, wash thoroughly.

Usual dose:

- Take ZOLINZA® exactly as prescribed by your doctor. The recommended dose of ZOLINZA® is 400 mg once a day.
  - Take all 4 capsules (100 mg each) by mouth once a day.
  - Swallow each capsule whole. Do not chew or break open the capsule.
  - Take ZOLINZA® after a meal.
- **Drink at least 8 glasses (8X250mL) of liquid every day to reduce the chances of dehydration**.
- Continue to take ZOLINZA® as long as your doctor prescribes it.

A lower dose may be recommended by your doctor based on your individual treatment needs (for example, if you have liver disease).

Overdose:
Do not take more than the prescribed dosage of ZOLINZA®. If you take more than the prescribed dosage, call your doctor, local emergency room, or poison control center right away.

Missed Dose:
If you miss a dose, take it as soon as you remember. If you do not remember until it is nearly time for your next dose, skip the missed dose and go back to your regular schedule. Do not take a double dose of ZOLINZA®.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The most common side effects with ZOLINZA® include:

- **Stomach problems,** including diarrhea, nausea, vomiting, loss of appetite, constipation, abdominal pain and weight loss.
- **Low blood cell counts:** Your doctor may want to do blood tests to check your blood counts.
  - **Low red blood cells.** Low red blood cells may make you feel tired, get tired easily, appear pale, and become short of breath.
  - **Low platelets.** Low platelets can cause unusual bleeding or bruising under the skin. You should call your doctor right away if this occurs.
- **Tiredness**
- **Changes in the way things taste and dry mouth**
- **Hair loss**
- **Chills**
- **Dizziness**
- **Difficulty in breathing**
- **Headache**
- **Increased blood creatinine**
- **Muscle spasms (pain and weakness)**
- **Proteinuria (the protein in the urine)**.

Tell your doctor if you develop:

- leg swelling, chest pain, or shortness of breath, which are signs of possible serious side effects.

- excessive vomiting or diarrhea.

These are not all the possible side effects of ZOLINZA®. For more information, ask your doctor or pharmacist. Talk to your doctor if you think you have side effects from taking ZOLINZA®.

If you experience any symptoms of a possible heart rhythm disturbance, such as dizziness, palpitations, fainting, or seizures, you should seek immediate medical attention.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptoms / Effects		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common	Blood clots in the lungs (symptoms such as chest pain or shortness of breath)			√
	Anemia (symptoms such as feeling tired, appearing pale, and shortness of breath		√	
Uncommon	Fainting		√	
	Infections of the blood (symptoms such as high fever, chills, headache, confusion, rapid breathing)			√
	Blood clots in the legs, arms (symptoms such as leg swelling, pain or tenderness)			√
	Bleeding in the digestive tract			√
	Stroke (symptoms such as numbness or weakness of the arms or legs, dizziness or confusion, slurred/loss of speech)			√
	Dehydration		√	
	Thrombocytopenia (easy bruising and increased bleeding)		√	

This is not a complete list of side effects. For any unexpected effects while taking ZOLINZA®, contact your doctor or pharmacist.

HOW TO STORE IT

Store at room temperature (15 °C – 30 °C). Do not store above 30°C (86°F).

Keep ZOLINZA® and all medicines safely away from children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701E
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect

or at Merck Canada Inc. by one of the following 2 ways:

- Call toll-free at 1-800-567-2594
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-496-9092, or
  - Mail to: Merck Canada Inc.
    Pharmacovigilance
    P.O. Box 1005
    Pointe-Claire - Dorval, QC H9R 4P8

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program or Merck do not provide medical advice.

MORE INFORMATION

This document plus the full Product Monograph, prepared for health professionals can be found at:
http://www.merck.ca
or by contacting the sponsor, Merck Canada Inc.,
at: 1-800-567-2594

This leaflet was prepared by Merck Canada Inc.

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