AUSTRALIAN PRODUCT INFORMATION

ZOLINZA®

(vorinostat)
Capsules

1 NAME OF THE MEDICINE

Vorinostat

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For the full list of excipients, see **Section 6.1 List of Excipients**.

3 PHARMACEUTICAL FORM

ZOLINZA (vorinostat) 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.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

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

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage

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

If patients are intolerant to therapy, 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.

No dosage adjustment is necessary for the elderly (see **Section 4.4 Special Warnings and Precautions for Use, Use in the elderly**).

In a phase I study to evaluate tolerability in non-CTCL cancer patients with hepatic impairment, the tolerated dose of ZOLINZA for those patients with mild and moderate hepatic dysfunction was 300 and 200 mg orally daily, respectively. (see **Section 4.4 Special Warnings and Precautions for Use, Use in hepatic impairment**).

4.3 CONTRAINDICATIONS

ZOLINZA is contraindicated in patients who:

- are hypersensitive to any component of this product
- have severe hepatic impairment.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Thromboembolism

As pulmonary embolism and deep vein thrombosis have been reported as adverse experiences, physicians should be alert to the signs and symptoms of these events, particularly in patients with a prior history of thromboembolic events (see **Section 4.8 Adverse Effects (Undesirable Effects), Serious adverse experiences**). Patients should be instructed about the signs of deep vein thrombosis and should consult their physician should any evidence of deep vein thrombosis develop.

Gastrointestinal

Patients should be instructed to drink at least 2 L/day of fluid to prevent dehydration and should promptly report excessive vomiting or diarrhoea to their physician. Gastrointestinal disturbances, including nausea, vomiting and diarrhoea have been reported (see **Section 4.8 Adverse Effects (Undesirable Effects)**) which may require the use of antiemetic and antidiarrhoeal medications. Fluid and electrolyte replacement should be administered to prevent dehydration (see **Section 4.8 Adverse Effects (Undesirable Effects)**). Pre-existing nausea, vomiting, and diarrhoea should be adequately controlled before beginning therapy with ZOLINZA.

Haematologic

Treatment with ZOLINZA is associated with dose-related thrombocytopenia and anaemia. If platelet counts and/or haemoglobin are severely reduced during treatment with ZOLINZA, the dose should be modified or therapy discontinued (See **Section 4.4 Special Warnings and Precautions for Use, Effects on laboratory tests, Section 4.8 Adverse Effects (Undesirable Effects)** and **Section 4.2 Dose and Method of Administration**). Patients receiving ZOLINZA should seek immediate medical attention if unusual bleeding occurs.

Hyperglycaemia

Hyperglycaemia has been observed in patients receiving ZOLINZA (see **Section 4.8 Adverse Effects (Undesirable Effects), Laboratory tests**). Serum glucose should be monitored, especially in diabetic or potentially diabetic patients. Adjustment of diet and/or anti-hyperglycaemic therapy may be necessary.

Use in hepatic impairment

ZOLINZA was studied in 42 non-CTCL cancer patients with hepatic impairment. Based on these results, ZOLINZA should be used with caution in patients with mild and moderate hepatic impairment, and is contraindicated in severe hepatic impairment (See **Section 4.3 Contraindications** and **Section 5.2 Pharmacokinetic Properties, Special populations, Hepatic insufficiency**).

Use in the elderly

In clinical studies, the efficacy and 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.

Paediatric use

The safety and effectiveness of ZOLINZA in paediatric patients have not been studied.

Effects on 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.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Vorinostat inhibits CYP drug metabolizing enzymes in human liver microsomes only at high concentrations (IC50 >75 µM). Gene expression and enzyme activity studies in human hepatocytes detected some potential for suppression of CYP2C9 and CYP3A4 activities by vorinostat at concentrations higher (≥10 µM) than clinically relevant concentrations. 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.

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.

Coumarin-Derivative Anticoagulants

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

ZOLINZA should not be administered concomitantly with other HDAC inhibitors (e.g. valproic acid) as class-specific adverse reactions may be additive. Severe (Grade 4) thrombocytopenia with associated gastrointestinal bleeding and anaemia has been reported with the concomitant use of ZOLINZA and valproic acid.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Effects on the female reproductive system were observed in rats, and included dose dependent increases in the number of corpora lutea at all doses (15, 50 or 150 mg/kg/day) and increased resorptions and dead fetuses at 150 mg/kg/day. Serum vorinostat AUC at 15 and 150 mg/kg/day in rats, based on the free fraction of vorinostat, was 0.3 and 2 times the mean clinical AUC at 400 mg/day, respectively.

Male fertility was unaffected at oral doses up to 150 mg/kg/day in rats. Sperm count and motility, testicular weight or testicular and epididymal histomorphology were unaffected. Testicular degeneration was observed in dogs at 100 mg/kg/day PO for 4 weeks, with plasma AUC 0.6 times the clinical AUC. No testicular findings were seen in the 6-month repeat dose study in dogs at plasma AUC 0.5 times the clinical AUC or repeat dose studies in rats for 6 months at plasma AUC approximately 2 times the clinical AUC.

Use in pregnancy

(Category D)

There are no adequate and well-controlled studies in pregnant women using ZOLINZA. 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 foetus.

Vorinostat crossed the placenta in rats and rabbits. No foetal malformations were observed in rats at oral doses at up to 50 mg/kg/day (≤1 times the human exposure based on AUC). There were, however, treatment-related developmental effects including decreased mean live foetal weights, incomplete ossifications (skull, thoracic vertebra and sternebra) and skeletal variations (cervical ribs, supernumeracry ribs, 20 vertebrae and sacral arch variations) at 50 mg/kg/day. In rabbits, the incidence of gallbladder malformations was increased at all doses tested (20 - 150 mg/kg/day; <0.1 to 0.6 times the human exposure). Additional findings in rabbits were reduced mean live foetal weights and an increased incidence of incomplete ossification of metacarpals at 150 mg/kg/day.

Use in lactation

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.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The safety of ZOLINZA was evaluated in 111 CTCL patients in two 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 (diarrhoea, nausea, anorexia, weight decreased, vomiting, constipation, decreased appetite), constitutional symptoms (fatigue, chills), haematologic abnormalities (thrombocytopenia, anaemia), and taste disorders (dysgeusia, dry mouth).

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 ≥10%)

	ZOLINZA 400 mg once daily (N=86)			
Adverse Experience	**All Grades**		**Grades 3-5***	
	n	**%**	**n**	**%**
Diarrhoea	39	45.3	0	0.0
Fatigue	39	45.3	2	2.3
Nausea	32	37.2	3	3.5
Thrombocytopenia	22	25.6	5	5.8
Anorexia	20	23.3	2	2.3
Dysgeusia	20	23.3	0	0.0
Weight Decreased	17	19.8	1	1.2
Dry Mouth	14	16.3	0	0.0
Alopecia	14	16.3	0	0.0
Muscle Spasms	13	15.1	2	2.3
Anaemia	11	12.8	2	2.3

Blood Creatinine Increased	10	11.6	0	0.0
Decreased Appetite	10	11.6	1	1.2
Vomiting	10	11.6	0	0.0
Chills	9	10.5	1	1.2
Constipation	9	10.5	0	0.0
* None of these adverse experiences were Grade 5.				

The adverse experience profile was generally similar in the remaining CTCL patients who received other doses. The frequencies of more severe thrombocytopenia, anaemia (see **Section 4.4 Special Warnings and Precautions for Use, Haematologic**) and fatigue were increased at doses higher than 400 mg once daily of ZOLINZA.

Serious Adverse Experiences

The most common serious drug-related adverse experiences in the 107 CTCL patients in two clinical studies (including all doses) were pulmonary embolism, reported in 4.7% (5/107) of patients, dehydration and thrombocytopenia each reported in 3.7% (4/107) and anaemia reported in 1.9% (2/107) of patients. There were single experiences of chest pain, death (of unknown cause), deep vein thrombosis, diarrhoea, gastrointestinal haemorrhage, hepatic ischaemia, hypotension, ischaemic stroke, nausea, pyrexia, streptococcal bacteraemia, syncope or vomiting.

Discontinuations

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 anaemia, angioneurotic oedema, asthenia, chest pain, death, deep vein thrombosis, ischaemic stroke, lethargy, pulmonary embolism and skin lesion.

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 experiences. These adverse experiences included increased serum creatinine, decreased appetite, hypokalaemia, 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).

Laboratory Tests

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. Hyperglycaemia 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 **Section 4.4 Special Warnings and Precautions for Use, Hyperglycaemia**).

Transient increases in serum creatinine were detected in 47.1% (41/87) of CTCL patients; in most cases these increases were non-severe, however, Grade III (severe) cases have been observed.

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 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 **Section 4.4 Special Warnings and Precautions for Use**, **Gastrointestinal** and **Effects on Laboratory tests**).

Adverse Experiences in Non-CTCL Patients

In addition to the 111 CTCL patients, 312 patients received ZOLINZA for solid tumors or non-CTCL haematologic malignancies 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, hyponatraemia, non-small cell lung cancer, tumor hemorrhage, Guillain-Barre syndrome, renal failure, urinary retention, cough, hemoptysis, hypertension and vasculitis.

In some patients recovering from surgery of the bowel, anastomotic healing adverse experiences have been reported. Therefore, caution should be exercised in the use of ZOLINZA in the perioperative period when patients require bowel surgery.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

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

In clinical studies, the highest total daily doses tested were 600 mg (once daily), 800 mg (400mg twice daily) and 900 mg (300 mg three times daily). In four patients who took more than the recommended study dose (without exceeding the highest doses tested), no adverse experiences were reported.

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 information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacology and pharmacological actions

Mechanism of action

Vorinostat is an 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 and transcription factors. The anti-neoplastic effect of vorinostat is attributed to the inhibition of HDAC activity and subsequent accumulation of acetylated proteins, including histones. Vorinostat induces cell cycle arrest, differentiation or apoptosis of some transformed cells *in vitro*. The mechanisms of action for the antineoplastic effect of vorinostat have not been fully characterized.

In vivo, vorinostat demonstrates anti-neoplastic activity in a variety of rodent tumor models including xenograft models of human prostate, breast and colon carcinoma.

Cardiac Electrophysiology

A randomized, partially-blind, placebo-controlled, 2-period crossover study was performed to assess the effects of a single 800-mg dose of vorinostat on the QTc interval in 24 patients with advanced cancer. This study was conducted to assess the impact of vorinostat on ventricular repolarization. The upper bound of the 90% confidence interval of the placebo-adjusted mean QTc interval change-from-baseline was less than 10 msec at every time point through 24 hours. Based on these study results, administration of a single supratherapeutic 800 mg dose of vorinostat does not appear to prolong the QTc interval in patients with advanced cancer; however the study did not include a positive control to demonstrate assay sensitivity. In the fasted state, oral administration of a single 800 mg dose of vorinostat resulted in a mean AUC and C_{max} and median T_{max} of 8.6±5.7 μM•hr and 1.7±0.67 μM and 2.1 (0.5-6) hours, respectively.

In clinical studies in patients with CTCL, 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.

Clinical trials

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

Advanced Cutaneous T-cell Lymphoma

In an open-label, single-arm, multicenter Phase IIb non-randomized study, 74 patients with advanced stage CTCL were treated with 400 mg once daily ZOLINZA. The primary endpoint was response rate of oral ZOLINZA in the treatment of skin disease 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. The population had been exposed to a median of three prior therapies (range 1 to 12). 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. Response had to be maintained for at least 4 weeks to be considered either CCR or PR.

Secondary endpoints included relief of pruritus; response duration; time to progression; time to objective response; and safety and tolerability.

The overall objective response 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 was 29.5% (18/61). One patient with Stage IIB CTCL achieved a CCR. Median time to response was 55 and 56 days (range 28 to 171 days), respectively, in the overall population and in patients with Stage IIB and higher 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 (See Table 2).

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 (see Table 2).

The median time-to-progression approached 5 months (148 days) for the overall population of 74 patients and exceeded 5 months (169 days) for patients with Stage IIB and higher CTCL. However the median time-to-progression was not reached in patients who responded to ZOLINZA and is estimated to exceed 7.5 months (see Table 2).

Table 2
Number of Patients Treated with ZOLINZA with an Objective Response
(All CTCL Patients)

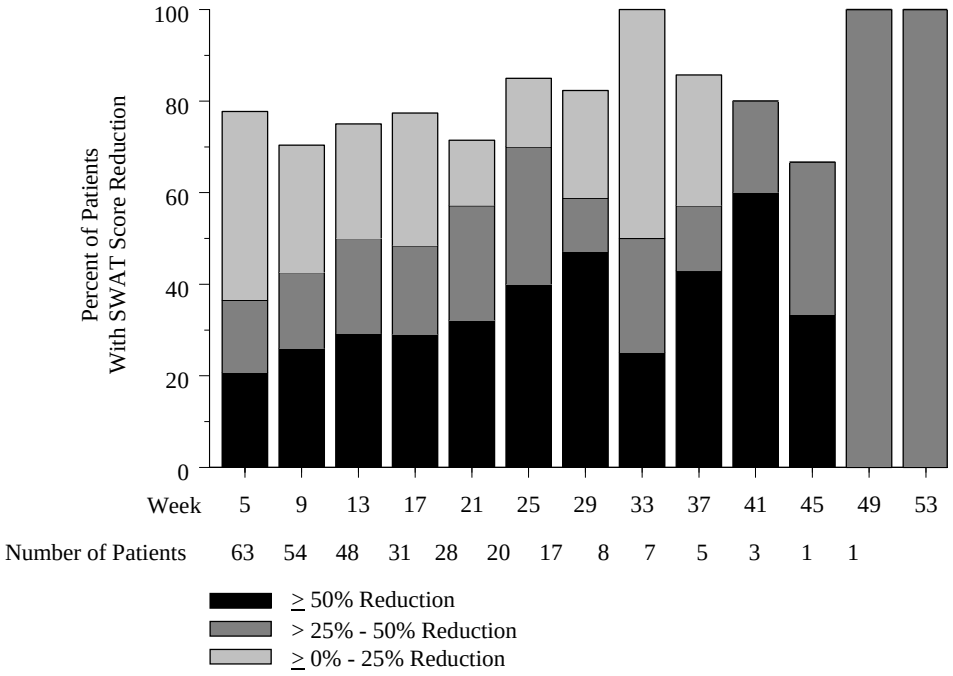
Population		**Patients Treated with ZOLINZA with an Objective Response**				
				Time to Objective Response† **(days)**	**Duration of Objective Response (days)**	**Time to Progressive Disease (days)**
	N	**n (%)**	**(95% CI)**	**Median (Range)**	**Median (Range)**	**Median (Range)**
All Patients	74	22 (29.7%)	(19.7, 41.5)	55 (28, 171)	NR (34+, 441+)	NR (78+, 470+)
Stage IIB or Higher‡	61	18 (29.5%)	(18.5, 42.6)	56 (28, 171)	NR (34+, 441+)	NR (85, 470+)
Patients with Sezary syndrome	30	10 (33.3%)	(17.3, 52.8)	56 (28, 171)	NR (34+, 244+)	NR (85, 365+)
Patients with T3 tumour disease	22	5 (22.7%)	(7.8, 45.4)	31 (29, 87)	187 (55, 441+)	NR (148, 470+)

† Objective Response: confirmed complete clinical response or partial response
‡ Stages IIB, III, IVA and IVB
CI = Confidence Interval
NR = Not reached
+ = Response ongoing

In addition to the 22 patients who had demonstrated an objective response, 10 patients with Stage IIB or higher CTCL and one patient with Stage IB had experienced stable disease, defined as absence of disease progression or absence of response, for 24 weeks. Therefore, 44.6% (33/74) of all patients and 45.9% (28/61) of patients with Stage IIB or higher CTCL demonstrated either objective response or 24 weeks of stable disease.
Improvement in skin disease, as measured by some (>0%) reduction in SWAT at any time point during treatment with ZOLINZA, was attained in 81.1% (60/74) of all patients treated with ZOLINZA.

The degree of improvement over time for patients over the course of the study is summarized in Figure 1.

Figure 1
Percent of Patients with a Reduction in SWAT Score from Baseline during the Study with ZOLINZA



Additional clinical benefit from ZOLINZA included a ≥25% reduction in Sezary cells in 51.9% (14/27) of patients with Sezary syndrome. For patients with palpable clinically abnormal lymph nodes, 41.7% (10/24) patients had a ≥50% reduction in the sum of the products of the greatest diameters of their index lymph nodes. In addition, 56.3% (9/16) of the patients with T3 tumor disease had a ≥50% reduction in body surface area covered by tumor.

The response to ZOLINZA was similar whether or not patients responded to previous bexarotene therapy or other last systemic therapy. The treatment just prior to ZOLINZA, either bexarotene or other therapies, had no obvious impact on the subsequent efficacy of ZOLINZA. Response to any previous systemic therapy does not appear to be predictive of response to ZOLINZA. This suggests that CTCL is not cross-resistant to ZOLINZA or to other available marketed and investigational therapies for CTCL.

Cutaneous T-cell Lymphoma

In an open-label, non-randomized Phase II study, ZOLINZA was evaluated to determine the response rate of patients with CTCL who were refractory to or intolerant of at least one conventional 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.

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. 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).

5.2 PHARMACOKINETIC PROPERTIES

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, 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 are approximately 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.

Paediatric

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

Hepatic Insufficiency

Vorinostat is contraindicated in patients with severe hepatic impairment and should be used with caution in patients with mild (total bilirubin >1.0x to 1.5x ULN or total bilirubin ≤ ULN and AST >ULN) and moderate (total bilirubin 1.5 - ≤3 x ULN) degrees of hepatic impairment. In a phase I study of non-CTCL patients with mild and moderate hepatic impairment, the tolerated daily dose, for patients is 300 and 200 mg orally daily respectively, due to dose-limiting toxicity of vorinostat.

In general, studies of vorinostat excluded patients with severe hepatic dysfunction. However, a limited number of patients with moderate hepatic dysfunction were enrolled in these studies. In a retrospective analysis of these clinical studies, a total of 48 out of 345 patients (13.9%) were identified as having potential liver function abnormality at enrollment. No clinically meaningful differences in hepatic adverse experiences were observed in patients with a history of hepatic abnormality compared to patients without a reported history of hepatic abnormality.

Renal Insufficiency

Vorinostat was not evaluated in patients with renal impairment. However, renal excretion does not play a role in the elimination of vorinostat.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Vorinostat induced gene mutations in the bacterial reverse mutation assays (Ames test), chromosome aberrations *in vitro* in Chinese hamster ovary (CHO) cells and chromosome damage in an *in vivo* micronucleus assay in mice. Vorinostat did not cause chromosome aberrations in human peripheral blood lymphocytes *in vitro*. Weight of evidence indicates vorinostat is a weakly genotoxic compound, except for chromosome damaging effects in CHO cells.

Carcinogenicity

Carcinogenicity studies have not been performed with vorinostat.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Each 100 mg capsule contains microcrystalline cellulose, croscarmellose sodium and magnesium stearate. The capsule shell include Empty Hard Gelatin Capsules Part #G3ICSRR0591 Size 3 White Opaque, OPACODE monogramming ink S-1-17822 BLACK and OPACODE monogramming ink S-1-17823 BLACK.

6.2 INCOMPATIBILITIES

Not applicable.

6.3 SHELF LIFE

The expiry date can be found on the packaging. In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG).

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C (86°F).

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 **Section 5.3 Preclinical Safety Data, Genotoxicity**).

6.5 NATURE AND CONTENTS OF CONTAINER

Zolinza (vorinostat) is available in bottles of 120 capsules.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

ZOLINZA (vorinostat) is a member of a new class of anti-neoplastic agents called histone deacetylase (HDAC) inhibitors. HDACs catalyze the removal of acetyl groups from the lysine residues of proteins, including histones.

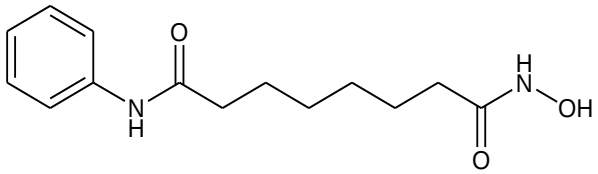
ZOLINZA contains vorinostat, which is described chemically as *N*-hydroxy-*N'*-phenyloctanediamide.

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.

The empirical formula is $C_{14}H_{20}N_2O_3$. The molecular weight is 264.32.

Chemical structure

The structural formula of vorinostat is:



CAS number

The CAS Registry number is 149647-78-9.

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8 SPONSOR

Merck Sharp & Dohme (Australia) Pty Limited
Level 1, Building A, 26 Talavera Road

Macquarie Park NSW 2113
www.msd-australia.com.au

9 DATE OF FIRST APPROVAL

17 December 2009

10 DATE OF REVISION

23 November 2023

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
	Addition of a company copyright statement

RCN: 000024941-AU

Copyright © 2023 Merck & Co., Inc., Rahway, NJ, USA, and its affiliates. All rights reserved.