

New drugs

Vorinostat

Approved indication: cutaneous T cell lymphoma
Zolinza (Merck Sharp & Dohme)
capsules containing 100 mg
Australian Medicines Handbook section 14.2.3

Cutaneous T cell lymphomas are non-Hodgkin lymphomas that occur in the skin but may involve lymph nodes, blood and visceral organs in more advanced disease. Most patients present with mycosis fungoides (patches, plaques, tumours or erythroderma) or Sézary syndrome (erythroderma with leukaemic involvement). There is no curative treatment, and goals for patients with advanced disease include preventing progression, inducing remission and improving their quality of life (for example relief from severe pruritus).

Vorinostat is an anticancer drug that inhibits histone deacetylases. Defective regulation of these enzymes has been identified in malignant cells, and restoring normal acetylation through inhibition may have an antitumour effect.

In an open-label phase II study, three dosing schedules of vorinostat were assessed in 33 patients who either had refractory disease or were intolerant of conventional treatments. Patients were assigned to doses of 400 mg once daily (group 1), 300 mg twice daily for three days a week (group 2), or 300 mg twice daily for two weeks followed by a week with no treatment then 200 mg twice daily (group 3). Response rates were assessed by calculating the percentage of total body surface area affected. Overall, eight patients (24%) had a partial response, defined as at least 50% reduction in skin involvement. No patients completely cleared their skin disease. Response rates were higher in groups 1 and 3, where patients received continuous treatment, compared to group 2 in which patients took vorinostat only three days a week (response rates: 31% and 33% vs 9%). Fourteen of the 31 patients with pruritus experienced symptomatic relief during the trial. Overall, the time to response varied between 3.6 and 21.9 weeks and the duration of response varied between 9.4 and 19.4 weeks. The median time to progression in the trial was 12.1 weeks.¹

Serious adverse events occurred in 14 patients and included dehydration, thrombocytopenia, vomiting,

anaemia, hypotension, infection, nausea, pulmonary embolism, fever and sepsis. The INR was increased in some patients on warfarin and decreased in others. Two patients died during the study – one as a consequence of disease progression and the other from untreated sepsis. Overall, the incidence of drug-related serious adverse events and discontinuations was lowest in patients who took vorinostat 400 mg once daily.¹

In another non-randomised open-label phase II trial, 74 patients with advanced refractory disease received oral vorinostat 400 mg daily. Average treatment duration was 5.3 months. Overall 30% of patients partially responded to vorinostat. One patient was completely clear of skin disease after 281 days of treatment. Around a third of patients reported they had experienced relief from pruritus. The median time to response was 55 days (28 to 171 days). The median duration of response end point was not reached but was estimated to be at least 185 days (34 to 441 days). The overall time to progression was 148 days. Survival of patients was not reported.² At study completion, 58 of the 74 patients had discontinued treatment – 49 of these withdrawals were due to lack of efficacy or progressive disease and nine were due to an adverse event.

The most common drug-related adverse events in the trial were diarrhoea (48.6% of patients), fatigue (45.9%), nausea (43.2%), anorexia (25.7%), taste disturbance (24.3%), thrombocytopenia (21.6%), weight decrease (20.3%), alopecia (17.6%), muscle spasms (16.2%), blood creatinine increase (14.9%), anaemia (12.2%), chills (12.2%), vomiting (12.2%), constipation (10.8%) and dry mouth (10.8%). Most of these were mild to moderate, but some such as fatigue, thrombocytopenia, nausea, anorexia and muscle spasms were more severe. Drug-related serious adverse events occurred in eight of the 74 patients. These included pulmonary embolism, deep vein thrombosis, anaemia, blood creatinine increase, dehydration, gastrointestinal haemorrhage, ischaemic stroke, streptococcal bacteraemia, syncope and thrombocytopenia. There were three deaths in the trial – one from disease progression (day 52), one secondary to a stroke (day 227) and one of unknown cause (day 2).²

One of three patients taking warfarin in the trial required a dose reduction to maintain target INR. ECG changes were observed in 15 patients, including three patients with a prolonged QTc interval.²



Some of the views expressed in the following notes on newly approved products should be regarded as preliminary, as there may be limited published data at the time of publication, and little experience in Australia of their safety or efficacy. However, the Editorial Executive Committee believes that comments made in good faith at an early stage may still be of value. Before new drugs are prescribed, the Committee believes it is important that more detailed information is obtained from the manufacturer's approved product information, a drug information centre or some other appropriate source.

NEW DRUGS

As thromboembolic events have been reported with vorinostat, doctors should be vigilant for the signs and symptoms, particularly in patients with a history of pulmonary embolism and deep vein thrombosis. Dose-related thrombocytopenia and anaemia can also occur so platelet counts and haemoglobin should be monitored. Dose reduction or discontinuation of treatment may be needed. Prothrombin time and INR were altered in some patients taking warfarin with vorinostat and should be monitored closely.

Increased serum glucose was found in two-thirds of patients taking vorinostat. Transient increases in serum creatinine were also detected in almost half of patients. Occasionally these increases were severe. Fortnightly chemistry tests, including electrolytes, glucose and serum creatinine, are recommended for the first two months of treatment, then monthly after that.

Nausea, vomiting and diarrhoea are not uncommon with vorinostat. These can lead to dehydration and patients should be advised to drink at least 2 L water a day. Treatments for nausea, vomiting and diarrhoea may be required. Vorinostat should not be given with other drugs that inhibit histone deacetylases, for example valproic acid, as adverse effects may be cumulative. Severe thrombocytopenia with gastrointestinal bleeding and anaemia has been reported with concomitant valproic acid use.

Following an oral dose of 400 mg with a high-fat meal, peak serum concentrations of vorinostat were reached after a median of 4 hours (2–10 hours). Absorption is lower in the fasted state so vorinostat should be given with food. Vorinostat is extensively metabolised but only 1% of metabolites are excreted renally. It is contraindicated in severe hepatic impairment and is not recommended for people with moderate hepatic impairment.

Vorinostat seems to have some benefit for up to a third of patients given the 400 mg daily dose, either by reducing the amount of skin affected or

relieving symptoms of pruritus. However, vorinostat is associated with serious adverse effects and it is not known if it actually extends the life of patients.^{1,2}

Although vorinostat has been approved in the USA since 2006, an application for its approval in Europe was withdrawn by the sponsor in 2008. This appeared to be in response to queries from the European Medicines Agency (EMA), which was concerned that the trials were non-randomised and that there was no comparator to vorinostat. In the absence of a randomised controlled trial, it is difficult to quantify the risk of thromboembolism with vorinostat, and the EMA concluded that the risks may outweigh the benefits. They were also concerned that there were no survival data from the trials.

T manufacturer provided the AusPAR and the product information

REFERENCES *†

1. Duvic M, Talpur R, Ni X, Zhang C, Hazarika P, Kelly C, et al. Phase 2 trial of oral vorinostat (suberoylanilide hydroxamic acid, SAHA) for refractory cutaneous T-cell lymphoma (CTCL). *Blood* 2007;109:31-9.
2. Olsen EA, Kim YH, Kuzel TM, Pacheco TR, Foss FM, Parker S, et al. Phase IIb multicenter trial of vorinostat in patients with persistent, progressive, or treatment refractory cutaneous T-cell lymphoma. *J Clin Oncol* 2007;25:3109-15.

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The Transparency score (**T**) is explained in 'New drugs: T-score for transparency', *Aust Prescr* 2014;37:27.

* At the time the comment was prepared, information about this drug was available on the website of the Food and Drug Administration in the USA (www.fda.gov).

† At the time the comment was prepared, a scientific discussion about this drug was available on the website of the European Medicines Agency (www.ema.europa.eu).