NEW DRUGS

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Ripretinib

Approved indication: gastrointestinal stromal tumours

Qinlock (Specialised Therapeutics)
50 mg tablets

Ripretinib is a tyrosine kinase inhibitor indicated for adults with advanced gastrointestinal stromal tumours who have already had treatment with at least three other kinase inhibitors (e.g. imatinib, sunitinib and regorafenib). These tumours often have oncogenic mutations in the tyrosine kinases or platelet-derived growth factor receptor alpha. This makes the kinases overactive and causes uncontrolled multiplication of the cells. Ripretinib is a switch-control kinase inhibitor which locks the kinases in an inactive state and prevents downstream signalling and cell proliferation.

The efficacy and safety of ripretinib as a fourth-line therapy has been investigated in a placebo-controlled trial called INVICTUS.[1] Patients were randomised to oral ripretinib 150 mg once a day (n=85) or a matching placebo (n=44) in conjunction with best supportive care. In the event of progressive disease, patients receiving ripretinib were permitted to increase the dose to 150 mg twice a day and patients receiving placebo could cross over to ripretinib. In the ripretinib group, 9.4% of patients (8/85) responded to treatment (all partial responses) versus none of the patients in the placebo group. Ripretinib also improved median progression-free survival (6.3 vs 1 month) and overall survival (median 15.1 vs 6.6 months) compared to placebo.

Dose interruption (23.5% of patients), dose reduction (7.1%) and permanent discontinuation (8.2%) of ripretinib because of an adverse reaction was common in the trial. The most frequently reported treatment-emergent adverse events were alopecia (52% of patients), fatigue (42%), nausea (39%), abdominal pain (36%), constipation (34%), myalgia (32%), diarrhoea (28%), decreased appetite (27%), palmar-plantar erythrodysaesthesia syndrome (21%) and vomiting (21%). Treatment-emergent laboratory abnormalities included increases in activated partial thromboplastin time (35% of patients), lipase (32%) and triglycerides (26%), and decreases in phosphate (26%) and calcium (23%). Elevations in blood bilirubin (22% of patients) and creatine phosphokinase (21%) were also observed.

Hypertension was reported in 14% of patients taking ripretinib – half of these cases were severe (grades 3–4). It is therefore important to monitor patients' blood pressure before and during treatment. Cutaneous squamous cell carcinoma and melanoma occurred in 4.7% and 2.4% of patients who received ripretinib, so skin assessment is also recommended.

Cardiac dysfunction, including cardiac failure, occurred in 1.7% of patients, with decreased ejection fraction (grade 3) in 3.4% of those who had echocardiograms. Ejection fraction should be assessed before starting ripretinib and treatment should be permanently discontinued if grade 3 or 4 left ventricular systolic dysfunction occurs.

The recommended dose of ripretinib is 150 mg once a day with or without food. Tablets should be taken at the same time each day. Following oral administration, peak plasma concentrations are reached after four hours and steady state is reached after 15 days. The elimination half-life is approximately 15 hours and the main route of excretion is via the faeces.

Ripretinib is mainly metabolised by cytochrome P450 (CYP) 3A4 so inhibitors and inducers of this enzyme could affect plasma concentrations. The drug is also a substrate of P-glycoprotein so inhibitors of this transporter may increase ripretinib exposure. Ripretinib and its metabolite (DP-5439) inhibit CYP2C8 so may affect other medicines that are cleared by this enzyme.

Based on the results of animal studies, ripretinib may affect fertility in men. It may also cause embryo–fetal harm (pregnancy category D drug) and should not be used in pregnancy. Breastfeeding is not recommended until at least a week after the final dose of ripretinib.

For patients with advanced gastrointestinal stromal tumours who have no other treatment options, ripretinib can improve survival by approximately eight months. However, it causes considerable adverse effects which can be treatment limiting.

T manufacturer provided the product information

REFERENCE

1. Blay J-Y, Serrano C, Heinrich MC, Zalcberg J, Bauer S, Gelderblom H, et al. Ripretinib in patients with advanced gastrointestinal stromal tumours (INVICTUS): a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Oncol 2020;21:923-34. https://doi.org/10.1016/s1470-2045(20)30168-6

The Transparency Score is explained in New drugs: transparency, Vol 37 No 1, Aust Prescr 2014;37:27.

At the time the comment was prepared, information about this drug was available on the websites of the Food and Drug Administration in the USA, the European Medicines Agency and the Therapeutic Goods Administration.