Palbociclib

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Approved indication: breast cancer

Ibrance (Pfizer)
75 mg, 100 mg or 125 mg capsules
Australian Medicines Handbook Appendix A

Palbociclib is indicated for people with advanced breast or metastatic cancer that is hormone-receptor positive (oestrogen and/or progesterone) and human epidermal growth factor receptor 2 (HER2)-negative. It is a small molecule inhibitor of cyclin-dependent kinases 4 and 6 and the first in its class to be approved in Australia. These kinases are involved in signalling pathways that lead to cell proliferation and their activity is increased in hormone-receptor-positive breast cancers.

When used as initial therapy, palbociclib should be given in combination with an aromatase inhibitor such as letrozole. However, in women who have progressed on previous endocrine-based therapy, it should be given with the oestrogen receptor antagonist fulvestrant.

The recommended dose of palbociclib is 125 mg with food at around the same time every day. It is given for 21 days of a 28-day cycle. Co-administered letrozole 2.5 mg should be given orally every day of the 28-day cycle and co-administered fulvestrant 500 mg should be given intramuscularly on days 1, 15 and 29 of the first cycle and then once a month after that. Before and during treatment, pre- and perimenopausal women should also be given a gonadotrophin-releasing hormone agonist such as goserelin.

The approval of palbociclib is based on several clinical trials.[1-4] An open-label phase 2 study (PALOMA-1) randomised previously untreated postmenopausal women to palbociclib plus letrozole (n=84) or letrozole alone (n=81). At the final analysis, median progression-free survival was longer in the group receiving combination treatment compared to the group receiving letrozole alone (20.2 vs 10.2 months).[1] Median overall survival was also longer (37.5 vs 34.5 months). In the palbociclib plus letrozole group, 42% of patients had a partial response to treatment and 1% had a complete response. The corresponding response rates in the letrozole-only group were 32% and 1%.[1]

Similar results were found in a double-blind trial (PALOMA-2) of previously untreated postmenopausal women (n=666). Median progression-free survival was longer with palbociclib plus letrozole compared to placebo plus letrozole (24.8 vs 14.5 months).[2]

Another trial enrolled 521 women who had relapsed or progressed despite previous endocrine therapy (PALOMA-3).[3] Unlike PALOMA-1 and -2, this trial compared palbociclib with fulvestrant and included pre- and perimenopausal women, who received concomitant goserelin. Following treatment with palbociclib plus fulvestrant or placebo plus fulvestrant, median progression-free survival was significantly longer in the palbociclib group (9.5 vs 4.6 months).[4]

In women receiving palbociclib and letrozole, the most common adverse events were neutropenia (78.9% of patients), infections (59.6%), leukopenia (40%), fatigue (38%), nausea (34.3%), alopecia (31.1%), stomatitis (29.4%), anaemia (26.4%) and diarrhoea (25.2%). The adverse event profile was similar in women who received fulvestrant with palbociclib.

Although rare, pulmonary embolism was more common in women taking palbociclib (1.15%, 10/872) than in women taking comparator treatments (0.63%, 3/473).[1-3] Eye problems including blurred vision, increased lacrimation and dry eye were also more common (3.4–6.4% vs 0.7–2.7%).

Myelosuppression is a problem with palbociclib. Neutropenia was serious (grade 3 or 4) in two-thirds of the women taking palbociclib in the trials. Complete blood counts need to be monitored before treatment starts, at the beginning of each cycle and on day 15 of the first two cycles. If severe neutropenia develops, the dose should be stopped or reduced, or the next treatment cycle should be delayed.

Following oral administration, maximum serum concentrations are reached in 4–8 hours. Palbociclib is extensively metabolised by oxidation and sulfonation. The drug's elimination half-life is 28.8 hours in patients with breast cancer and the dose is eliminated in the faeces (74.1%) and urine (17.5%). Exposure to palbociclib is increased in renal and hepatic impairment.

Palbociclib is mainly metabolised by cytochrome P450 (CYP) 3A and sulfotransferase enzyme (SULT2A1). Concomitant administration of strong CYP3A inhibitors (e.g. atazanavir, clarithromycin, erythromycin, voriconazole and grapefruit juice) is not recommended. Strong CYP3A inducers (e.g. carbamazepine, phenytoin, rifampicin, St John's wort) should also be avoided. Moderate CYP3A inducers such as efavirenz and modafinil can be used if absolutely necessary.

Palbociclib seems to extend progression-free survival when added to letrozole or fulvestrant in women who have hormone-receptor-positive and HER2-negative advanced or metastatic breast cancer. However, the addition of palbociclib carries the risk of severe and treatment-limiting myelosuppression for the majority of patients.

T manufacturer provided the product information

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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.