PDL NEW DRUG REVIEW

Proprietary Name: Ibrance®
Common Name: palbociclib
PDL Category: Antineoplastics-Kinase Inhibitors

Comparable Products	Preferred Drug List Status
Afinitor	Recommended

Summary

Indications and Usage: In combination with letrozole for the treatment of postmenopausal women with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer as initial endocrine-based therapy for their metastatic disease. This indication is approved under accelerated approval based on progression-free survival (PFS). Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

While there was no pregnancy category provided, the risk summary indicated that treatment can cause fetal harm if given to pregnant women per findings in animals and the mechanism of action. Women of reproductive potential should be advised to use effective contraception during treatment and for at least 2 weeks after the last dose. The safety and efficacy of use in children have not been established.

Dosage Forms: Capsules, 75mg, 100mg, and 125mg

Recommended Dosage: 125mg QD with food X21 consecutive days, followed by 7 days off treatment to comprise a complete 28 day cycle; should be taken in combination with letrozole 2.5mg QD given continuously for the 28 day cycle. Dose modifications are based on individual safety and tolerability, and to manage some adverse reactions which may require temporary dose interruptions and/or dose reductions, or discontinuation of treatment. Please refer to the prescribing information for specific information on recommended management for adverse reactions, hematologic toxicities, and non-hematologic toxicities.

Dose adjustments are not required for those with mild hepatic or mild to moderate renal impairment. Effects in those with moderate or severe hepatic impairment as well as severe renal impairment have not been studied.

Drug Interactions: As palbociclib is mainly metabolized by CYP3A, the concomitant use with strong CYP3A inhibitors (e.g. clarithromycin, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, verapamil, and voriconazole) should be avoided; however, if coadministration with a strong CYP3A inhibitor cannot be avoided, reduce the Ibrance® dose to 75mg QD. If the strong inhibitor is discontinued, increase the dose to the dose used prior to the initiation of the CYP3A inhibitor.

Avoid grapefruit or grapefruit juice with Ibrance®. Avoid the concomitant use of strong CYP3A inducers (e.g. phenytoin, rifampin, carbamazepine, and St. John's Wort) and moderate CYP3A inducers (e.g. bosentan, efavirenz, etravirine, modafinil, and nafcillin). The dose of sensitive CYP3A substrates with a narrow therapeutic index (e.g. alfentanil, cyclosporine, dihydroergotamine, ergotamine, everolimus, fentanyl, pimozide, quinidine, sirolimus, and tacrolimus) may need to be reduced if used concomitantly with Ibrance®.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Ibrance® plus letrozole) minus reported % incidence for letrozole monotherapy. Please note that an incidence of 0% means the incidence was the same or that the active drug was less than its comparator.* The most frequently reported adverse events included upper respiratory infections (13%), neutropenia (70%), leukopenia (40%), anemia (28%), thrombocytopenia (16%), decreased appetite (9%), peripheral

neuropathy (8%), epistaxis (10%), stomatitis (18%), nausea (12%), diarrhea (11%), vomiting (11%), alopecia (19%), fatigue (18%), and asthenia (9%).

Reported lab abnormalities included white blood cells decreased (69%), neutrophils decreased (77%), lymphocytes decreased (46%), hemoglobin decreased (43%), and platelets decreased (45%).

Contraindications: None listed

Manufacturer: Pfizer Laboratories, a division of Pfizer Inc

Analysis: Palbociclib, the active ingredient of Ibrance®, is a kinase inhibitor. Specifically, it is an inhibitor of cyclin-dependent kinase (CKD) 4 and 6, which are downstream of signaling pathways which lead to cellular proliferation. In vitro, palbociclib reduced cellular proliferation of estrogen receptor (ER)-positive breast cancer cell lines. The combination with letrozole increased the inhibition of retinoblastoma protein (Rb) phosphorylation, downstream signaling and tumor growth as compared to each drug alone.

An open-label, multicenter phase II study assessed the safety and efficacy of Ibrance® plus letrozole as compared with letrozole alone in postmenopausal women with ER-positive, HER2-negative advanced breast cancer who had not received previous systemic treatment for advanced disease. Treatment was given until progressive disease, unmanageable toxicity, or consent withdrawal. The primary efficacy outcome was investigator-assessed progression-free survival (PFS) according to Response Evaluation Criteria in Solid Tumors Version 1.0 (RECIST). Overall response rate in those with measurable disease was higher in the Ibrance®/letrozole group vs the letrozole group alone (55.4% vs 39.4%). At the final analysis of PFS, overall survival (OS) data was not mature with 37% of events. Median OS was improved (37.5 vs 33.3 months, respectively; p=0.81).[3] The table below illustrates results of the primary outcome, which was adapted from the prescribing information.

	Ibrance® + letrozole (N=84)	letrozole (N=81)
Number of Progression-free Survival (PFS) events	41 (48.8%)	59 (72.8%)
Hazard ratio	0.488; p=0.0004	
Median PFS (months)	20.2	10.2

In the study, there were more reports of Grade 3-4 neutropenia in the Ibrance®/letrozole group vs letrozole monotherapy (54% vs 1%), as well as leucopenia (19% vs 0%, respectively), and fatigue (4% vs 1%).

Place in Therapy: Ibrance® was approved under accelerated approval as first-line endocrine-based treatment in combination with letrozole for postmenopausal women with estrogen receptor positive, HER2-negative metastatic breast cancer. One noted reference source suggests the use of endocrine therapy rather than chemotherapy as initial therapy for most patients with ER-positive breast cancer. Treatment should be individualized.[3]

It is recommended that Ibrance® be added to the Recommended Drug List as recommended since it is considered a first-line treatment.

PDL Placement: ☒ **Recommended**
☐ **Non-Recommended**

References

[1] Ibrance [package insert]. New York, NY: Pfizer Labs, a division of Pfizer Inc; 2015.

[2] Finn RS, Crown JP, Lang I, et al. The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of estrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomized phase 2 study. *Lancet Oncol*. 2015; 16(1): 25-35.

[3] UpToDate desktop version. Treatment approach to metastatic hormone receptor-positive breast cancer: endocrine therapy. Accessed June 2015.