

Pharmaceutical Approval Update

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Letrozole (Femara)

Manufacturer: Novartis, Inc., East Hanover, NJ

Indication: Originally approved for the treatment of postmenopausal women with hormone-sensitive early breast cancer, letrozole can now be used immediately after surgery (in the adjuvant setting) to prevent cancer recurrence.

Drug Class: Letrozole is an aromatase inhibitor that blocks the enzyme aromatase from converting androgen to estrogen. This action causes reduced estrogen levels in the bloodstream, prevents estrogen from reaching estrogen receptors, and blocks the growth of cancer cells. Estrogen is thus prevented from stimulating the growth of hormone receptor-positive breast cancer. In postmenopausal women, most of the body's estrogen is made from another hormone, androgen.

Uniqueness of Drug: The phase 3 Breast International Group (BIG 1-98) trial compared the effectiveness and tolerability of letrozole and tamoxifen citrate (Nolvadex, AstraZeneca) when used as initial therapy after surgery for this population of women. Letrozole reduced the risk of breast cancer recurrence by an additional 21% ($P = .002$) over the reduction offered by tamoxifen. Patients taking letrozole also showed a 27% reduction in the risk of metastasis ($P = .0012$).

Letrozole demonstrated its greatest benefit in two groups of women at increased risk of recurrence. Letrozole therapy reduced this risk by 29% in women whose breast cancer had already spread to the lymph nodes at the time of diagnosis and by 30% in women who had undergone chemotherapy. In these high-risk subgroups, letrozole reduced the risk of metastasis by 33% and 31%, respectively.

Warnings: Letrozole may cause fetal harm when administered to pregnant women. At doses equal to or greater than 0.003 mg/kg (about 1/100 of the daily maximum recommended human dose), when administered to rats during the period of organogenesis, letrozole was toxic, as indicated by intrauterine mortality, increased resorption, increased post-implantation loss, decreased numbers of live fetuses; it also resulted in fetal anomalies.

Letrozole is also teratogenic in rats. A 0.03-mg/kg dose (about 1/10 the daily maximum recommended human dose) caused a domed head and cervical/centrum vertebral fusion in the fetus.

Letrozole was toxic to rabbit embryos at doses equal to or greater than 0.002 mg/kg and was toxic to rabbit fetuses when administered at a dosage of 0.02 mg/kg (about 1/100,000 and 1/10,000 the daily maximum recommended human dose). Fetal anomalies included incomplete ossification of the skull, sternbrae, forelegs, and hindlegs.

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Precautions: Fatigue and dizziness have been observed with the use of letrozole tablets. Somnolence was not commonly reported, but caution is advised for patients who drive or use machinery.

Laboratory Tests: No dose-related effects on any hematological or clinical chemistry parameters were evident. Moderate decreases in lymphocyte counts of uncertain clinical significance were observed in some patients receiving letrozole 2.5 mg. This depression was transient in about 50% of those affected. Two patients who were using letrozole developed thrombocytopenia; this relationship to the study drug was unclear.

Few patients with abnormal laboratory findings, whether or not these were related to the study treatment, withdrew from the trial.

Increases in alanine and aspartate transaminases (ALT, AST) and gamma-glutamyl-transferase (GGT) at or above five times the upper limit of normal (ULN) and of bilirubin at or equal to 1.5 times the ULN were most often associated with metastatic disease in the liver. About 3% of study participants receiving the study drug had abnormalities in liver chemistries not associated with documented metastases; these abnormalities may have been related to drug therapy.

By contrast, about 8% of patients receiving megestrol acetate (Megace, Bristol-Myers Squibb) and 10% of patients treated with aminoglutethimide (Cytadren, Novartis) had abnormalities in liver chemistries that were not associated with documented liver metastases.

Drug Interactions: In studies of cimetidine (Tagamet, GlaxoSmithKline) and warfarin (Coumadin, Bristol-Myers Squibb), the coadministration of letrozole with these drugs did not result in clinically significant drug interactions.

The administration of letrozole and tamoxifen 20 mg daily resulted in reduced letrozole plasma levels by 38% on average. No data are yet available to document the use of letrozole in combination with other anticancer agents.

Hepatic Insufficiency: Patients with cirrhosis and severe hepatic dysfunction who received letrozole at a dose of 2.5 mg experienced approximately twice the exposure to letrozole as healthy volunteers with normal liver function. Therefore, a lower dose is recommended for these patients. The effect of hepatic impairment on letrozole exposure in cancer patients with elevated bilirubin levels has not been determined.

Dosage and Administration:

Adults and Elderly Patients: The recommended dose is one 2.5-mg letrozole tablet once a day, without regard to meals. Treatment should continue until tumor progression is evident. No dose adjustment is required for older adults. Patients taking letrozole do not require glucocorticoid or mineralocorticoid replacement therapy.

Renal Impairment: No dosage adjustment is required for patients with renal impairment if the creatinine clearance is 10 ml/minute or more.

Hepatic Impairment: No dosage adjustment is recom-

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mended for patients with mild-to-moderate hepatic impairment, although letrozole blood concentrations were modestly increased in the subjects with moderate hepatic impairment caused by cirrhosis. The dose of letrozole in patients with cirrhosis and severe hepatic dysfunction should be reduced by 50%. The recommended dose of letrozole tablets for these patients is 2.5 mg administered every other day. The effect of hepatic impairment on letrozole exposure in noncirrhotic cancer patients with elevated bilirubin levels has not been established.

Commentary: Women who have gone through menopause now have another option for treating early-stage breast cancer and staving off recurrences. Letrozole fared better than tamoxifen, the long-favored treatment, in women of all ages. It is free of the more worrisome adverse effects of tamoxifen, such as endometrial cancer and potentially fatal blood clots. However, letrozole and other aromatase inhibitors are not without problems. Women receiving letrozole were more likely to experience osteoporosis and higher cholesterol levels.

Letrozole is the only agent in its class approved for use as an initial treatment immediately after surgery for hormone-sensitive early breast cancer and following the completion of five years of tamoxifen therapy.

Sources: www.pharmacyonesource.com; www.ca.novartis.com

Lenalidomide (Revlimid)

Manufacturer: Celgene Corporation, Summit, NJ

Indication: Lenalidomide has been approved for the treatment of patients with transfusion-dependent anemia caused by low-risk or intermediate-risk myelodysplastic syndromes (MDSs) associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities.

Drug Class: Lenalidomide, 3-(4-amino-1, 3-dihydro-1-oxo-2H-isoindol-2-yl)-2, 6-piperidinedione, is an analogue of thalidomide.

Uniqueness of Product: Lenalidomide is an immunomodulatory agent with antiangiogenic properties. The drug inhibits the secretion of pro-inflammatory cytokines and increases the secretion of anti-inflammatory cytokines from peripheral blood mononuclear cells.

Warnings:

Potential for Birth Defects. Lenalidomide is an analogue of thalidomide, a known teratogen that causes severe life-threatening human birth defects. If lenalidomide is taken during pregnancy, it may cause birth defects or death to the fetus. Women should be advised to avoid pregnancy while taking lenalidomide.

Special Prescribing Requirements. Because of the potential for toxicity and birth defects, lenalidomide is available under a restricted distribution program called "Rev-assist." Only health care professionals and pharmacists registered with the program are permitted to prescribe the product. Lenalidomide may be dispensed only to patients who are registered and who meet all the conditions of the program.

Hematological Toxicity. Lenalidomide is associated with significant neutropenia and thrombocytopenia. Patients should

undergo a complete blood cell count weekly for the first eight weeks of lenalidomide treatment and at least monthly thereafter to monitor cytopenia. Most patients with the deletion 5q MDS abnormality required a dose adjustment for neutropenia and/or thrombocytopenia.

Thromboembolic Events. Lenalidomide is associated with a significant risk of deep vein thrombosis and pulmonary embolism in patients with multiple myeloma. Patients should be carefully observed for signs and symptoms of thromboembolism and are advised to seek medical care immediately if shortness of breath, chest pain, or swelling of the arms or legs develops.

Other Adverse Events. Common adverse events included diarrhea, pruritus, rash, fatigue, constipation, nausea, nasopharyngitis, arthralgia, pyrexia, back pain, peripheral edema, cough, dizziness, headache, muscle cramps, dyspnea, and pharyngitis.

Because the majority of lenalidomide is excreted by the kidneys, the risk of toxic reactions may be greater in patients with impaired renal function.

Dosage and Administration: The recommended starting dose of lenalidomide is 10 mg/day orally with water. Patients should not break, chew, or open the capsule. Dosing is continued according to clinical and laboratory findings.

Commentary: The FDA's approval of lenalidomide applies to patients with a particular genetic mutation on one chromosome that results in the inability of the bone marrow to produce enough normal red blood cells and blood-clotting platelets. To remain healthy, patients with this type of MDS require periodic blood and platelet transfusions and antibiotics for the treatment of infections.

Lenalidomide was effective in patients with the dislocated section of a chromosome that results in MDS. Thus, oral therapy that treats the 5q MDS abnormality may be able to reduce or even eliminate the need for red blood cell transfusions in these patients.

The warnings for lenalidomide use are completely appropriate in view of the drug's chemical structure and history of problems with thalidomide. Because the agent is derived from thalidomide, which caused severe birth defects in the 1950s, Celgene plans to market lenalidomide under a special risk-management plan to ensure that it will not be available to women who might become pregnant. Lenalidomide is a promising agent for other types of oncological disease.

Sources: www.pharmacyonesource.com; www.revlimid.com

Abatacept (Orencia)

Manufacturer: Bristol-Myers Squibb, Princeton NJ

Indication: Abatacept is indicated to reduce the signs and symptoms of rheumatoid arthritis (RA) by inducing a major clinical response in patients. A major clinical response is defined as maintaining an American College of Radiology (ACR) score of 70 for six months.

This product slows the progression of structural damage and improves physical function in adults with moderate to severely active RA who have had an inadequate response to methotrexate or tumor necrosis factor-alpha (TNF- α) blockers.

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Biological Class: Abatacept is a fully human soluble fusion protein that blocks a costimulatory signal required for T-cell activation.

Uniqueness of Drug: Abatacept is the first approved agent to demonstrate efficacy and safety in patients with an inadequate response to TNF- α antagonists as well as those with an inadequate response to methotrexate.

Warnings: Concurrent therapy with abatacept and disease-modifying antirheumatic drugs (DMARDs) is not recommended. Combining abatacept with TNF- α antagonists increased the occurrence of infections and provided no additional relief of symptoms. In controlled clinical trials, patients receiving abatacept plus TNF- α antagonists, such as etanercept (Enbrel), adalimumab (Humira), and infliximab (Remicade), experienced more treatment-related infections (63%) and serious infections (4.4%) than patients receiving TNF- α antagonists alone (43% and 0.8%, respectively).

Precautions: Caution should be exercised in patients with a history of infection or underlying conditions that predispose them to infections. Abatacept should be discontinued if a serious infection develops. Patients should be screened for tuberculosis. If the result is positive, they should receive standard medical care before they begin therapy with abatacept.

Fewer than 1% of patients treated with abatacept experienced hypersensitivity reactions, including two cases of ana-

phylaxis or anaphylactoid reactions. Other events potentially associated with drug hypersensitivity (e.g., hypotension, urticaria, and dyspnea) occurred in fewer than 0.9% of the treated patients, and they generally occurred within 24 hours of an infusion. Appropriate medical support measures for the treatment of hypersensitivity reactions should be available.

Live vaccines should not be given concurrently with abatacept or within three months of discontinuing the agent.

Patients with chronic obstructive pulmonary disease (COPD) who received abatacept experienced adverse effects more often than patients taking placebo, including COPD exacerbations, cough, bronchitis, and dyspnea. Abatacept should be prescribed with caution for patients with RA and COPD. These patients should be monitored for worsening of their respiratory status.

Abatacept should be used during pregnancy only if it is essential.

Dosage and Administration: Abatacept is given as a 30-minute intravenous infusion. It is administered at two and four weeks after the first infusion, then every four weeks thereafter. It may be used as monotherapy or concomitantly with DMARDs other than TNF- α antagonists.

Each vial provides 250 mg of abatacept. For patients weighing less than 60 kg, the dose is 500 mg (two vials). For patients weighing 60 to 100 kg, the dose is 750 mg (three vials). For patients weighing more than 100 kg, the dose is 1 g (four vials).

Commentary: Rheumatoid arthritis (RA) is a systemic, chronic, autoimmune disease characterized by inflammation in the lining of joints (synovium), causing joint damage with chronic pain, stiffness, and swelling. Abatacept offers improved physical function for patients who have not achieved an adequate response from anti-TNF- α therapy for active RA.

Results suggest that abatacept will have a great impact on patients with RA. As a selective costimulation modulator, abatacept can block the initiation and stimulation of T cells and down-regulate activated T cells, which are essential for the initiation and maintenance of RA.

Sources: www.pharmacyonesource.com; www.bms.com; www.arthritispractitioner.com ■