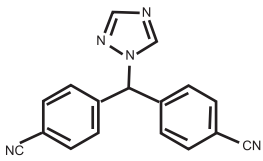
Senora Tablets

سینورا ٹیبلٹس

COMPOSITION: ***Each film coated tablet contains:*** Letrozole BP/USP 2.5 mg.

DESCRIPTION: Senora (letrozole tablets) for oral administration contains 2.5 mg of letrozole, a nonsteroidal aromatase inhibitor (inhibitor of estrogen synthesis). It is chemically described as 4, 4'-(1H-1, 2, 4-Triazol-1-ylmethylene)dibenzonitrile, and its structural formula is



Letrozole is a white to yellowish crystalline powder, practically odorless, freely soluble in dichloromethane, slightly soluble in ethanol, and practically insoluble in water. It has a molecular weight of 285.31, empirical formula $C_{17}H_{11}N_5$ and a melting range of 184°C-185°C.

CLINICAL PHARMACOLOGY: ***Mechanism of Action:*** The growth of some cancers of the breast is stimulated or maintained by estrogens. Treatment of breast cancer thought to be hormonally responsive (i.e., estrogen and/or progesterone receptor positive or receptor unknown) has included a variety of efforts to decrease estrogen levels (ovariectomy, adrenalectomy, hypophysectomy) or inhibit estrogen effects (antiestrogens and progestational agents). These interventions lead to decreased tumor mass or delayed progression of tumor growth in some women. In postmenopausal women, estrogens are mainly derived from the action of the aromatase enzyme, which converts adrenal androgens (primarily androstenedione and testosterone) to estrone and estradiol. The suppression of estrogen biosynthesis in peripheral tissues and in the cancer tissue itself can therefore be achieved by specifically inhibiting the aromatase enzyme. Letrozole is a nonsteroidal competitive inhibitor of the aromatase enzyme system; it inhibits the conversion of androgens to estrogens. In adult nontumor- and tumor-bearing females, letrozole is as effective as ovariectomy in reducing uterine weight, elevating serum LH, and causing the regression of estrogen-dependent tumors. In contrast to ovariectomy, treatment with letrozole does not lead to an increase in serum FSH. Letrozole selectively inhibits gonadal steroidogenesis but has no significant effect on adrenal mineralocorticoid or glucocorticoid synthesis. Letrozole inhibits the aromatase enzyme by competitively binding to the heme of the cytochrome P450 subunit of the enzyme, resulting in a reduction of estrogen biosynthesis in all tissues Treatment of women with letrozole significantly lowers serum estrone, estradiol and estrone sulfate and has not been shown to significantly affect adrenal corticosteroid synthesis, aldosterone synthesis, or synthesis of thyroid hormones.

PHARMACOKINETICS: ***Absorption and Distribution:*** Letrozole is rapidly and completely absorbed from the gastrointestinal tract and absorption is not affected by food. It is metabolized slowly to an inactive metabolite whose glucuronide conjugate is excreted renally, representing the major clearance pathway. About 90% of radiolabeled letrozole is recovered in urine. Letrozole's terminal elimination half-life is about 2 days and steady-state plasma concentration after daily 2.5mg dosing is reached in 2-6 weeks. Plasma concentrations at steady state are 1.5 to 2 times higher than predicted from the concentrations measured after a single dose, indicating a slight non-linearity in the pharmacokinetics of letrozole upon daily administration of 2.5 mg. These steady-state levels are maintained over extended periods, however, and continuous accumulation of letrozole does not occur. Letrozole is weakly protein bound and has a large volume of distribution (approximately 1.9 L/kg). ***Metabolism and Excretion:*** Metabolism to a pharmacologically-inactive carbinol metabolite (4,4'-methanol-bisbenzonitrile) and renal excretion of the glucuronide conjugate of this metabolite is the major pathway of letrozole clearance. Of the radiolabel recovered in urine, at least 75% was the glucuronide of the carbinol metabolite, about 9% was two unidentified metabolites, and 6% was unchanged letrozole. In human microsomes with specific CYP isozyme activity, CYP3A4 metabolized letrozole to the carbinol metabolite while CYP2A6 formed both this metabolite and its ketone analog. In human liver microsomes, letrozole strongly inhibited CYP2A6 and moderately inhibited CYP2C19.

PHARMACODYNAMICS: In postmenopausal patients with advanced breast cancer, daily doses of 0.1 mg to 5 mg SENORA suppress plasma concentrations of estradiol, estrone, and estrone sulfate by 75%-95% from baseline with maximal suppression achieved within two-three days. Suppression is dose-related, with doses of 0.5 mg and higher giving many values of estrone and estrone sulfate that are below the limit of detection in the assays. Estrogen suppression is maintained throughout treatment in all patients treated at 0.5 mg or higher. Letrozole is highly specific in inhibiting aromatase activity. There is no impairment of adrenal steroidogenesis.The blockade of estrogen biosynthesis does not lead to accumulation of androgenic precursors. Plasma levels of LH and FSH and thyroid function is not affected by letrozole.

INDICATIONS AND USAGE: ***Adjuvant Treatment of Early Breast Cancer:*** SENORA (letrozole) is indicated for the adjuvant treatment of postmenopausal women with hormone receptor positive early breast cancer. ***Extended Adjuvant Treatment of Early Breast Cancer:*** SENORA is indicated for the extended adjuvant treatment of early breast cancer in postmenopausal women, who have received 5 years of adjuvant tamoxifen therapy. ***First and Second-Line Treatment of Advanced Breast Cancer:*** SENORA is indicated for first-line treatment of postmenopausal women with hormone receptor positive or unknown, locally advanced or metastatic breast cancer. SENORA is also indicated for the treatment of advanced breast cancer in postmenopausal women with disease progression following antiestrogen therapy.

CONTRAINDICATIONS: SENORA may cause fetal harm when administered to a pregnant woman and the clinical benefit to premenopausal women with breast cancer has not been demonstrated. SENORA is contraindicated in women who are or may become pregnant. If SENORA is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

ADVERSE REACTIONS: The most common adverse reactions (greater than 20%) are hot flashes, arthralgia, flushing, asthenia, edema, headache, dizziness, hypercholesterolemia, increase sweating and bone pain.

DRUG INTERACTIONS: ***Tamoxifen:*** Coadministration of SENORA and tamoxifen 20 mg daily resulted in a reduction of letrozole plasma levels.The therapeutic effect of SENORA therapy is not impaired if SENORA is administered immediately after tamoxifen. ***Cimetidine:*** A pharmacokinetic interaction with cimetidine shows no clinically significant effect on letrozole pharmacokinetics. ***Warfarin:*** An interaction with warfarin shows no clinically significant effect of letrozole on warfarin pharmacokinetics. ***Other Anticancer Agents:*** There is no clinical experience to date on the use of SENORA in combination with other anticancer agents.

WARNINGS AND PRE CAUTIONS: ***Bone Effects:*** Use of SENORA may cause decreases in bone mineral density (BMD .)Consideration should be given to monitoring BMD. ***Cholesterol:*** Consideration should be given to monitoring serum cholesterol. ***Hepatic Impairment:*** Patients with cirrhosis and severe hepatic impairment who are dosed with 2.5 mg of SENORA may experience approximately twice the exposure to SENORA as healthy volunteers with normal liver function. Therefore, a dose reduction is recommended for this patient population. The effect of hepatic impairment on SENORA exposure in cancer patients with elevated bilirubin levels has not been determined. ***Fatigue and Dizziness***: Senora can cause fatigue, dizziness, and somnolence. Caution is advised when driving or using machinery until it is known how the patient reacts to SENORA use. ***Laboratory Test Abnormalities:*** No dose-related effect of SENORA on any hematologic or clinical chemistry parameter is evident. Moderate decreases in lymphocyte counts, of uncertain clinical significance, may observe in some patients receiving Senora 2.5 mg.

SPECIAL POPULATIONS: ***Pregnancy:*** SENORA may cause fetal harm when administered to a pregnant woman and the clinical benefit to premenopausal women with breast cancer has not been demonstrated. SENORA is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to fetus. ***Lactation:*** It is not known if letrozole is present in human milk. There are no data on the effects of letrozole on the breastfed infant or milk production. Advise lactating women not to breastfeed while taking SENORA and for at least 3 weeks after the last dose. ***Pediatric Use:*** The safety and effectiveness in pediatric patients have not been established. ***Geriatric Use:*** Patients greater than or equal to 70 years of age may experience longer time to tumor progression and higher response rates than patients less than 70. ***Hepatic Impairment:*** Breast cancer patients with severe hepatic impairment are thus expected to be exposed to higher levels of letrozole than patients with normal liver function receiving similar doses of this drug.

DOSAGE AND ADMINISTRATION: ***Recommended Dose:*** The recommended dose of SENORA is one 2.5 mg tablet administered once a day, without regard to meals. ***Use in Adjuvant Treatment of Early Breast Cancer:*** In the adjuvant setting, the optimal duration of treatment with letrozole is unknown. Treatment should be discontinued at relapse. ***Use in Extended Adjuvant Treatment of Early Breast Cancer:*** In the extended adjuvant setting, the optimal treatment duration with SENORA is not known. The treatment should be discontinued at tumor relapse. ***Use in First and Second-Line Treatment of Advanced Breast Cancer:*** In patients with advanced disease, treatment with SENORA should continue until tumor progression is evident. ***Use in Hepatic Impairment:*** No dosage adjustment is recommended for patients with mild to moderate hepatic impairment, although SENORA blood concentrations are modestly increased in patients with moderate hepatic impairment due to cirrhosis. The dose of SENORA in patients with cirrhosis and severe hepatic dysfunction should be reduced by 50%. The recommended dose of SENORA for such patients is 2.5 mg administered every other day. The effect of hepatic impairment on SENORA exposure in noncirrhotic cancer patients with elevated bilirubin levels has not been determined. ***Use in Renal Impairment:*** No dosage adjustment is required for patients with renal impairment if creatinine clearance is greater than or equal to 10 mL/min.

OVERDOSAGE: No serious adverse reactions are reported However, emesis could be induced if the patient is alert. In general, supportive care and frequent monitoring of vital signs are also appropriate.

STORAGE/PRECAUTIONS: Store in a cool, dry and dark place between 15-30 °C. Keep all medicines out of the reach of children. To be used on the prescription of Registered Medical Practitioners.

PRESENTATION: SENORA Tablets 2.5 mg are available in packing containing 10 film coated tablets.

خوراک: ڈاکٹر کی ہدایت کے مطابق۔

احتیاط: روشنی، نمی اور گرمی سے بچائیں۔ 15 سے 30 ڈگری سینٹی گریڈ کے درمیان محفوظ کریں۔ تمام ادویات بچوں کی پہنچ سے دور رکھیں۔ مستند ڈاکٹر کے نسخہ پر فروخت اور استعمال کریں۔

Complete Medical Information available only for doctors on request.

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5-D, I-10/3 Industrial Area, Islamabad-Pakistan.
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