PRESCRIBING INFORMATION: To be sold by retail on the prescription of Psychiatrist only.

ENDOXIFEN TABLETS 8 mg
ZONALTA

1. GENERIC NAME
Endoxifen tablets 8 mg
2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each enteric coated tablet contains:
Endoxifen Citrate 12.12 mg
equivalent to Endoxifen 8 mg
Excipients: Q.S.
Colours: Titanium Dioxide, Iron Oxide Yellow and
FD&C Blue #2/ Indigo Carmine Aluminum Lake
3. DOSAGE FORM AND STRENGTH
Enteric coated tablet 8 mg
4. CLINICAL PARTICULARS
4.1 Therapeutic indications
Endoxifen is indicated for the acute treatment of manic episodes with or without mixed features of Bipolar I disorder.
4.2 Dosage and method of administration
Endoxifen 8 mg tablet is given orally once daily. Simultaneous consumption of grapefruit should be avoided.
The efficacy of endoxifen was established in 3-week trials with patients meeting DSM-V criteria for bipolar I disorder and currently displaying an acute manic episodes with or without mixed features. Healthcare providers who prescribe endoxifen for extended periods should continually reevaluate the long-term usefulness of the drug for the individual patient.
4.3 Contraindications
Endoxifen is contraindicated in patients who have a history of hypersensitivity to tamoxifen or any of the constituents of endoxifen citrate. Endoxifen is contraindicated in patients who require concomitant coumarin-type anticoagulant therapy or in patients with a history of deep vein thrombosis or pulmonary embolus.
4.4 Warnings and Precautions
Endoxifen, being an active metabolite of tamoxifen, warnings and precautions of tamoxifen will also be applicable to endoxifen citrate and hence, the same have been mentioned here accordingly.
Hematologic Events
Hematological effects of endoxifen administered orally are not known. However, thrombolism may be more common in patients treated with tamoxifen, though this is not certain, as patients with cancer are at increased risk anyway. A small reduction in antithrombin III concentration was noted in a study of 11 post-menopausal women treated with tamoxifen, and no significant reduction was seen in a group of premenopausal women. There is evidence of an increased incidence of thromboembolic events, including deep vein thrombosis and pulmonary embolism, during tamoxifen citrate therapy.
Endocrine and Reproductive Systems
Endoxifen's anti-estrogenic adverse events in pre or post-menopausal women are unknown. However, the anti-estrogenic effects of tamoxifen in pre-menopausal women receiving therapeutic doses can cause irregular menses. Anti-estrogenic adverse effects in women treated with tamoxifen include vasomotor symptoms (hot flushes), vaginal bleeding and pruritis vulvae.
Effects on the Uterus-Endometrial Cancer and Uterine Sarcoma
An increased incidence of uterine malignancies has been reported in association with tamoxifen citrate treatment. The underlying mechanism is unknown, but may be related to the estrogen-like effect of tamoxifen citrate. Most uterine malignancies seen in association with tamoxifen citrate are classified as adenocarcinoma of the endometrium. However, rare uterine sarcomas, including malignant mixed mullerian tumors (MMMT), have also been reported.
Non-Malignant Effects on the Uterus
Increased incidences of endometrial changes including hyperplasia and polyps have been reported in association with tamoxifen citrate treatment. There have been a few reports of endometriosis and uterine fibroids in women receiving tamoxifen citrate. Ovarian cysts have also been observed in a small number of premenopausal patients with advanced breast cancer who have been treated with tamoxifen citrate. Tamoxifen citrate has also been reported to cause menstrual irregularity or amenorrhea.
Hepatic effects
Tamoxifen citrate has been associated with changes in liver enzyme levels, and on rare occasions, a spectrum of more severe liver abnormalities including fatty liver, cholestasis, hepatitis and hepatic necrosis. Few cases of liver cancer have been reported with tamoxifen citrate in clinical trials.
Effects on the Eye
Ocular disturbances, including corneal changes, decrement in color vision perception, retinal vein thrombosis, and retinopathy have been reported in patients receiving tamoxifen citrate. An increased incidence of cataracts and the need for cataract surgery have been reported in patients receiving tamoxifen citrate.
Pregnancy Category D
There are no adequate and well-controlled trials of endoxifen and tamoxifen in pregnant women. There have been a small number of reports of vaginal bleeding, spontaneous abortions, birth defects, and fetal deaths in pregnant women with tamoxifen citrate. If endoxifen is used during pregnancy or the patient becomes pregnant while taking this drug, or within approximately two months after discontinuing therapy, the patient should be apprised of the potential risks to the fetus including the potential long-term risk of a DES-like syndrome.
General
Decreases in platelet counts, usually to 50,000-100,000/mm^3, infrequently lower, have been occasionally reported in patients taking tamoxifen citrate for breast cancer. In patients with significant thrombocytopenia, rare hemorrhagic episodes have occurred, but it is uncertain if these episodes are due to tamoxifen citrate therapy. Leukopenia has been observed, sometimes in association with anemia and/or thrombocytopenia. There have been rare reports of neutropenia and pancytopenia in patients receiving tamoxifen citrate; this can sometimes be severe. Hypercalcemia has been reported in some breast cancer patients with bone metastases within a few weeks of starting treatment with tamoxifen citrate. If hypercalcemia does occur, appropriate measures should be taken and, if severe, endoxifen citrate should be discontinued.
Monitoring during endoxifen therapy
Women taking or having previously taken endoxifen citrate should be instructed to seek prompt medical attention for new breast lumps, vaginal bleeding, gynecologic symptoms (menstrual irregularities, changes in vaginal discharge, or pelvic pain or pressure), symptoms of leg swelling or tenderness, unexplained shortness of breath, or changes in vision. Women should inform all care providers, regardless of the reason for evaluation, that they take endoxifen citrate.
4.5 Drug Interactions
No information is currently available regarding the pharmacologic interaction of endoxifen with other medical products.
When tamoxifen citrate is used in combination with coumarin-type anticoagulants, a significant increase in anticoagulant effect may occur. Where such coadministration exists, careful monitoring of the patient's prothrombin time is recommended. Hence, careful monitoring is also recommended during coadministration of coumarin-type anticoagulants with endoxifen. Drugs that are inducers/inhibitors of cytochrome P 450 isozymes, may be expected to have little effect on endoxifen clearance because cytochrome P450 enzymes do not metabolize it. Drugs that elevate the levels of glucuronosyl transferase may increase the clearance of endoxifen.
4.6 Use in special populations (such as pregnant women, lactating women, pediatric patients, geriatric patients etc.)
Pregnancy & Lactation
While there have been no clinical trials to assess its reproductive toxicity, endoxifen may cause fetal harm when administered to pregnant women. Endoxifen should not be administered to women who are pregnant or nursing. A pregnancy test must be performed prior to starting treatment, and all patients must be instructed to use effective contraception during the treatment with endoxifen.
Geriatric Patients
Safety and effectiveness in geriatric patients have not been established.
Pediatric Patients
Safety and effectiveness in pediatric patients have not been established.
Renal Impairment
Safety and effectiveness in patients with renal impairment have not been established.
Hepatic Impairment
Safety and effectiveness in patients with hepatic impairment have not been established.
4.7 Effects on ability to drive and use machines:
Endoxifen is unlikely to impair the ability of patients to drive or operate machinery. However, fatigue has been reported with the use of tamoxifen and caution should be observed when driving or using machinery while such symptoms persist.
4.8 Undesirable effects
A total of 63 adverse events (AEs) were reported by 27 patients during conduct of phase II clinical study - 59 were mild, 02 were moderate, and 02 were severe in intensity. The causality was assessed as possible for 07 AEs, probable for 26 AEs, unlikely for 20 AEs, and unrelated for 10 AEs associated with the study drugs administered. Total 63 AEs were reported as following: 19 AEs in endoxifen 4 mg arm, 11 AEs in endoxifen 8 mg arm and 33 AEs in divalproex 1000 mg arm. The most frequently reported AEs (in descending order of occurrence) were insomnia, headache, nausea, dyspepsia, decreased appetite, and delusion. There were no deaths, other significant AEs or serious AEs reported during the conduct of phase II clinical study. Other side effects were: anemia, back pain, dizziness, dyskinesia, gastritis, hypertension, abnormal lipids, mouth ulceration, myalgia, nasopharyngitis, pain, restlessness, pustular rash, skin burning sensation, stomatitis and vomiting.
In phase III study a total of 100 adverse events (AEs) were reported by 64 patients where 72 AEs were mild, 27 were moderate and 1 was severe in nature. The causality was assessed as probable / likely for 34 AEs, as possible for 33 AEs, as unrelated for 14 AEs, as unlikely for 11 AEs and as related for 8 AEs to the endoxifen administered. Out of 100, 48 AEs were reported after administration of Test Product-Endoxifen. The most frequently reported AEs with endoxifen (in descending order of occurrence) were headache, vomiting, insomnia, worsening of mania. There were no deaths, serious or significant AEs during the conduct of the trial. Other side effects were: gastritis, epigastric discomfort, diarrhoea, restlessness, somnolence etc. The list of adverse events reported in phase III clinical trial in Test Product and Reference Product are in the table below:

Adverse events (as per MedDRA PT – Version 20.1)	Investigational Medicinal Product		
	Endoxifen arm	Divalproex sodium arm	Total
Abdominal pain	1	3	4
Abdominal pain upper	0	1	1
Anxiety	0	1	1
Back pain	1	0	1
Blood pressure decreased	1	0	1
Blood thyroid stimulating hormone increased	0	2	2
Chest pain	0	1	1
Constipation	0	1	1
Decreased appetite	0	1	1
Depression	2	0	2
Diarrhoea	1	0	1
Dizziness	0	6	6
Dysuria	0	1	1
Epigastric discomfort	1	1	2
Fatigue	0	1	1
Flank pain	0	1	1
Gastritis	2	0	2
Gastroesophageal reflux disease	0	1	1
Headache	12	5	17
Hordeolum	1	0	1
Hypertriglyceridaemia	0	1	1
Insomnia	4	5	9
Leukopenia	1	0	1
Liver disorder	1	0	1
Mania*	4	3	7
Nasopharyngitis	0	1	1
Nausea	1	1	2
Pain	0	1	1
Paraesthesia	0	1	1
Platelet count decreased	0	1	1
Pruritus	1	0	1
Pyrexia	1	4	5
Restlessness	3	0	3
Social avoidant behaviour	1	0	1
Somnolence	1	2	3
Toothache	1	1	2
Upper respiratory tract infection	1	1	2
Vomiting	6	4	10
Total	**48**	**52**	**100**

*Worsening of disease
Following common side effects of tamoxifen can also be expected with endoxifen: Hot flushes, menstrual disturbances, discomfort in the pelvis, vaginal bleeding, itching around the vagina, vaginal discharge, stomach upsets (including nausea and vomiting), headaches, light-headedness, fluid retention (possibly seen as swollen ankles), bruising more easily, pain or tenderness in upper abdomen, skin rash or itching or peeling skin, hair and nail loss, yellow eyes, disturbances of vision or difficulties in seeing properly (possibly due to cataracts, change to the cornea or disease of the retina), cases of optic nerve diseases have been reported and, in a small number of cases, blindness has occurred, breathlessness and cough (inflammation of the lungs), pain, swelling or redness of the calf or leg which may indicate a blood clot, chest pain or shortness of breath which may indicate a blood clot, leg cramps and symptoms of a stroke. Other side effects not listed above may also occur in some patients who are on long term therapy; for example, endometrial cancer.
4.9 Overdose
No clinical experience with patients receiving an accidental overdose of endoxifen or an antidote is known. If such a case occurs, the patient should be carefully monitored and appropriate supportive care measures should be initiated.
5. PHARMACOLOGICAL PROPERTIES
5.1 Mechanism of action
The exact mechanism by which endoxifen exerts its therapeutic effects have not been established in Bipolar disorder I (BPD I). However, the efficacy of endoxifen could be mediated through Protein kinase C (PKC). The PKC represents a family of enzymes highly enriched in brain, where it plays a major role in regulating both pre- and post-synaptic aspects of neurotransmission. Excessive activation of PKC results in symptoms related to bipolar disorder. The PKC signaling pathway is clearly a target for the actions of two structurally dissimilar antimanic agents – lithium and valproate. Endoxifen exhibits four-fold higher potency in inhibiting PKC activity compared to tamoxifen in preclinical studies and is not dependent on the isozyme cytochrome P450 2D6 (CYP2D6) for action on the target tissues.
5.2 Pharmacodynamic Property
Phase II Trial:
Double blind, double dummy study was conducted to assess the efficacy and safety of endoxifen in bipolar I disorder patients with current manic or mixed episode.
In this dose escalation study, two dose levels of endoxifen were compared with standard of care (divalproex sodium extended release). In stage I, 27 and 15 patients were randomized to endoxifen 4 mg and divalproex 1000 mg arm respectively. In stage II of this study, 28 and 14 patients were randomized in endoxifen 8 mg and divalproex 1000 mg arm respectively. The primary efficacy endpoint used in this study was the response rate based on the YMRS (Young Mania Rating Scale) total score.

Response rates in Per Protocol (PP) data analysis were 45.87%, 64.29% and 77.78% in endoxifen 4 mg, endoxifen 8 mg and divalproex 1000 mg arm, respectively. P value of difference between the endoxifen 8 mg and divalproex 1000 mg arms (p = 0.3753) was found to be non-significant. A similar result also was obtained from the ITT (Intention to treat) data analysis.

Depressive symptoms were also assessed with the MADRS score (Montgomery Asberg Depression Rating Scale) throughout the trial. In the PP set of analysis, mean (± SD) reduction in the MADRS score was 3.21 (±2.449), 5.21 (±6.663) and 5.74 (±6.502) in endoxifen 4 mg, endoxifen 8 mg and divalproex 1000 mg arm, respectively.

At the end of three-week study treatment, the CGI-S (Clinical Global Impression- Severity of Illness scale) scores of most patients in all arms showed reductions indicative of no illness to mild illness states. Similar results were also observed on the CGI - Global Improvement scale score in all arms. The score of majority of the patients shifted to 'very much improved' and 'much improved' categories in all arms.

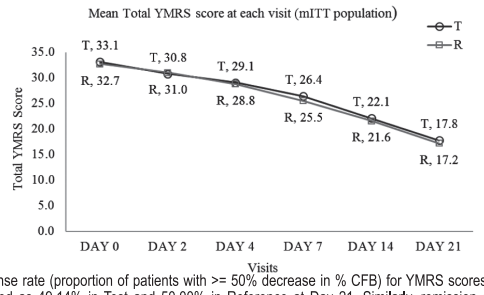
Phase III Confirmatory Trial:

Double-blind, double-dummy, active-controlled, oral, multiple-dose, parallel, randomized study was conducted to establish efficacy and safety of endoxifen in bipolar I disorder patients.

In this multicentric study, total 228 patients (116 patients in the Test (T) - 8 mg endoxifen arm and 112 patients in the Reference (R) -1000 mg divalproex sodium extended release arm) were enrolled for three week (21 days) duration. A safety follow-up was performed after 2 weeks (Day 35) for all the patients.

Mean change in total YMRS (Young Mania Rating Scale) score at Day 21 against baseline (primary endpoint) was 15.59 and 15.76 (Point estimate: -0.17 & 95% CI: -2.50 - 2.16) in test & reference arms, respectively, which proved the non-inferiority.

Plot for mean Total YMRS score at each visit for modified intention-to-treat (mITT) population has been presented below.

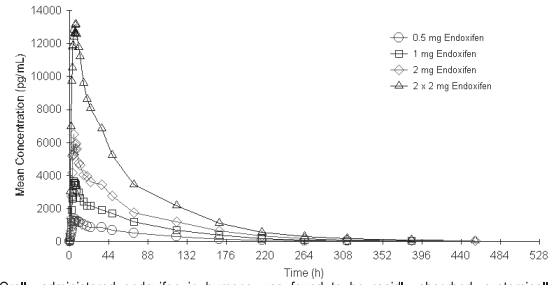


Response rate (proportion of patients with >= 50% decrease in % CFB) for YMRS scores was observed as 49.14% in Test and 50.00% in Reference at Day 21. Similarly, remission (Total YMRS score ≤ 12), composite remission (YMRS Total Score ≤ 12 and MADRS Score ≤ 10) and cumulative remission (proportion of patients that attained YMRS score ≤ 12 at a given visit and maintained it at all subsequent double-blind visits) were similar in both the groups.

There was no statistical significant difference observed between comparison of treatments (i.e. Test vs. Reference) in change from baseline to Day 21 for Clinical Global Impression-Bipolar (CGI-BP) score and for CGI-S score. MADRS score were reduced significantly in both the groups; however, the reduction was comparable (Test arm: 2.3 and reference arm: 2.9; P value 0.3867).

5.3 Pharmacokinetic properties

The pharmacokinetics of endoxifen was evaluated at escalating single doses in 40 male and female healthy adult human subjects. The plasma concentration profiles of endoxifen at different doses are shown in the figure below:



Orally administered endoxifen in humans was found to be rapidly absorbed, systemically available and exhibited linear pharmacokinetics. Endoxifen displays dose-proportional PK with respect to C_{max} and $AUC_{0-infinity}$. The time to peak (T_{max}) were between 4.5 and 6 h. Endoxifen exhibited linear pharmacokinetics (0.5 – 4.0 mg).

A multiple-dose escalating study was also conducted in patients with metastatic breast cancer. Endoxifen at 3 dose levels (2, 4, or 8 mg) was given once daily for 28 days. At steady state, it displayed dose-proportional pharmacokinetics with respect to C_{max} and AUC (see Table below).

Pharmacokinetic Parameters of Endoxifen in Metastatic Breast Cancer Patients after Multiple-dose Administration of 2, 4 or 8 mg Endoxifen Tablets

	Mean ± SD		
Parameters (units)	2 mg (n=5)	4 mg (n=5)	8 mg (n=5)
T_{max} (h)*	5 (3.0-12.0)	5 (4.0-6.0)	5 (4.0-6.0)
$C_{min,ss}$ (ng/ml)	15.7 ±6.4	44.0±11.6	80.4±26.7
$C_{max,ss}$ (ng/ml)	24.5 ±7.3	75.9 ±18.5	134.1 ±32.1
$AUC_{tau,ss}$ (ng.h/ml)	445.3 ±146.2	1363.3 ±396.3	2322.6 ±619.8
PTF(%)	50.8 ±19.0	56.5 ±17.9	57.6 ±14.6
$C_{av,ss}$ (ng/ml)	18.6±6.1	56.8±16.5	96.8±25.8

*T_{max} is represented value of median and range

Half-life ($t_{1/2}$) values were 52.1–58.1 h for all doses. Inter-patient variability in pharmacokinetic parameters was approximately similar across the doses.

Absorption

Orally administered endoxifen in humans is rapidly absorbed and systemically available. The rate and extent of absorption of endoxifen increased linearly and in a manner proportional to the dose of endoxifen.

Distribution

Endoxifen is highly bound to plasma proteins. The estimated volume of distribution (Vz) of endoxifen is about 400 L.

Metabolism

Endoxifen is not metabolized by Cytochrome P450 enzymes. It is eliminated by conjugation reactions in liver including sulphation (endoxifen-sulphate) and glucuronidation (endoxifen – O-Glucuronide).

Elimination

The Clearance (CL) of endoxifen is about 5 L per hour and is not affected by dose increase.

6. Nonclinical properties

Subchronic 28-day toxicity study in mice

Endoxifen citrate was well tolerated and no mortality was observed in any dose group including control throughout the dosing period of 28 days.

Endoxifen citrate was administered daily to male and female mice at the dose levels of 0.2 mg/kg, 0.4 mg/kg, 0.8 mg/kg and 8 mg/kg for a period of 28 days. At necropsy, no abnormalities detected in all the dose groups at the end of the treatment period. Gross pathological examination also did not reveal any abnormalities related to the treatment group. Histopathological examination revealed mild to moderate atrophy of seminal vesicles and prostate in male animals, mild follicular cysts, absence of corpora lutea and increased number of follicles in ovaries.

Mild to moderate epithelial hypertrophy of endometrial and myometrial glands, mild to moderate dilatation of myometrial glands and moderately reduced stromal cells were observed in uterus of female animals from 8 mg/kg dose group. Absence of corpora lutea in ovaries and minimal to moderate epithelial hypertrophy of endometrial and myometrial glands, minimal to moderate dilatation of myometrial glands and moderately reduced stromal cells of uterus were observed in female animals from all tested dose groups. All the above changes observed are suggestive of estrogenic effect of the endoxifen citrate.

Subchronic 28-day toxicity study in rats

Endoxifen citrate was well tolerated and no mortality was observed in any dose group including control throughout the dosing period of 28 days.

Endoxifen citrate was administered daily to the male and female Sprague-Dawley rats at the dose levels of 0.2 mg/kg, 0.4 mg/kg, 0.8 mg/kg and 4 mg/kg for a period of 28 days. Histological effect mainly reduced weight of uterus and mild to moderate atrophy of myometrial glands of uterus in female animals suggestive of estrogen effect of endoxifen citrate.

Subchronic 120-day toxicity study in mice

Endoxifen citrate was safe at a dose level of 0.5, 1 and 2 mg/kg body weight for 120 days in mice.

A study was conducted to assess the toxicity of endoxifen in mice following once daily administration of endoxifen citrate for 120 days at three dose levels: 0.5, 1 and 2 mg per kg body weight. A total of 40 male and 40 female mice were randomized into 4 dose groups having 10 male and 10 female mice in each group: Group A (Control, 0 mg/kg), Group B (0.5 mg/kg), Group C (1 mg/kg) and Group D (2 mg/kg). Animals were observed throughout 120 day dosing period for mortality and clinical signs of toxicity. There were no abnormalities contributed to endoxifen citrate detected on histopathological findings.

Subchronic 90-day toxicity study in Rabbit

Daily oral administration of endoxifen up to 1.0 mg/kg for 90 days did not show any toxicity in New Zealand White Rabbit. Overall, endoxifen citrate was well tolerated and no mortality was observed in any dose group including control throughout the dosing period of 90 days.

The objective of this study was to evaluate the effects of endoxifen when administered to New Zealand White Rabbit by oral route after repeated exposure for 90 days with 28 days recovery period. Six groups of Zealand White Rabbit comprising 4 males and 4 females per group were orally administered with endoxifen at dose levels of 0.25 (G3), 0.5 (G4), 1.0 (G5) mg/kg body weight for a period of 90 days. A concurrent control group (G1) comprising the 4 male and 4 female was also maintained in the study. In addition a high dose recovery group (G6 -1.0 mg/kg body weight) & control recovery group (G2-0 mg/kg body weight) with 4 male and 4 female were treated for 90 days and kept under observation for another 28 days in order to find out the persistence, recovery and delayed effect of endoxifen, if any.

Male Fertility study

The male fertility index at highest treated group of endoxifen was found to be similar compared to vehicle control group. Endoxifen citrate was administered orally to male Sprague Dawley rats at the dose levels of 0, 0.008, 0.04 and 0.2 mg/kg/day for 51 days. The reduction in sperm motility was observed at 0.2 mg/kg/day (high dose) that returned to normal values when endoxifen citrate was withdrawn for 4 weeks. The effect of endoxifen citrate on testicular development and on sperm production and fertility in humans is unknown.

Genotoxicity study

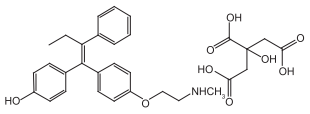
Endoxifen citrate was found to be "non-mutagenic" in the Bacterial Reverse Mutation Test up to the highest tested concentration of 5 mg/plate under the test conditions.

In Mammalian Chromosome Aberration Test, endoxifen citrate was found to be nonclastogenic up to the dose of 0.031 mg/mL, both in the presence and absence of metabolic activation under the test conditions.

A Mammalian Erythrocyte Micronucleus Test of endoxifen citrate was performed on Swiss Albino Mice and it was found to be non-mutagenic up to 2000 mg/kg body weight.

7. Description

Endoxifen (4-hydroxy-N-desmethyl tamoxifen) is an active metabolite of a selective estrogen receptor modulator (SERM), tamoxifen. Endoxifen appears as a white to off white powder which is soluble in methanol and ethanol and supplied as a citrate salt. The chemical name is(Z)-4-(1-(4-(2-(methylamino)ethoxy) phenyl)-2-phenylbut-1-en-1-yl)phenol Citrate; its empirical formula is C, 65.83; H, 6.24; N, 2.48; O, 25.46. Molecular weight of endoxifen citrate and endoxifen is 565.61 g/mol and 373.26 g/mol respectively. Its structural formula is as following:



8. Pharmaceutical particulars

8.1 Incompatibilities: Not applicable

8.2 Shelf-life: 3 years

8.3 Packaging information: ZONALTA Tablets are available in strip of 7 tablets.

8.4 Storage and handing instructions: **Store below 30°C and protect from moisture.**

9. Patient Counselling Information

Advise the patients to read the approved patient labeling (Patient Information). Endoxifen, being an active metabolite of tamoxifen, may cause the adverse events associated with tamoxifen.

Hematologic Events

Inform patient that endoxifen may increase the risk of thromboembolic events. Advise patients to seek medical attention immediately if signs or symptoms of a thromboembolic event occur with endoxifen treatment.

Endocrine and Reproductive Systems

Inform patients that anti-estrogenic effects of tamoxifen in pre-menopausal women receiving therapeutic doses may cause irregular menses. Anti-estrogenic adverse effects in women treated with tamoxifen include vasomotor symptoms (hot flushes), vaginal bleeding and pruritis vulvae. Advise patients to seek medical attention if these symptoms occur with endoxifen treatment.

Effects on the Uterus-Endometrial Cancer and Uterine Sarcoma

Inform patient that increased incidence of uterine malignancies has been reported in association with tamoxifen citrate treatment.

Non-Malignant Effects on the Uterus

Inform patient that increased incidences of endometrial changes including hyperplasia and polyps have been reported in association with tamoxifen citrate treatment.

Hepatic effects

Inform patients that tamoxifen citrate has been associated with changes in liver enzyme levels, and on rare occasions, a spectrum of more severe liver abnormalities including fatty liver, cholestasis, hepatitis and hepatic necrosis. These changes may occur with endoxifen treatment as well.

Effects on the Eye

Inform patient that ocular disturbances, including corneal changes, decrement in color vision perception, retinal vein thrombosis, and retinopathy may be observed in patients receiving endoxifen citrate.

Embryo-Fetal Toxicity

Advise pregnant women and females of reproductive potential that exposure during pregnancy or within 2 months prior to conception can result in fetal harm, including the potential long-term risk of a DES-like syndrome. Advise females to inform their healthcare provider of a known or suspected pregnancy.

Lactation

Advise women not to breastfeed during treatment and for 3 months after the last dose of endoxifen.

Manufactured by:

INTAS

INTAS PHARMACEUTICALS LTD.

Matoda-382 210, Dist.: Ahmedabad. INDIA

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