

HORMONAL THERAPY

ABARELIX (PLENAXIS®)

I. MECHANISM OF ACTION

Abarelix is a synthetic antagonist of luteinizing hormone–releasing hormone (LHRH). Abarelix causes an immediate inhibition of the hypothalamic–pituitary–gonadal axis that subsequently inhibits the production of testosterone and estrogen. The ability to achieve and maintain castrate testosterone concentrations is similar for abarelix and GnRH agonist use alone or with an antiandrogen. The uniqueness of abarelix is the absence of an initial increase in serum testosterone or estrogen concentration with drug receipt and the rapid achievement of sex hormone suppression.

II. PHARMACOKINETICS

- A) Administered intramuscularly. A subcutaneous (SC) formulation and administration via the SC route is under investigation. The peak serum concentration from IM use occurs approximately 3 days after administration.
- B) Distribution– extensive; 96–99% protein bound;
Note: Obese patients that weigh > 225 pounds have a greater decrease in overall effectiveness with increased abarelix duration of treatment.
- C) Metabolism– no evidence of hepatic microsomal cytochrome P450 enzyme involvement.
- D) Excretion: elimination half–life of abarelix 100 mg IM 13.2 ± 3.2 days. 13% of the dose was excreted in the urine as unchanged drug.

III. DOSAGE AND ADMINISTRATION

100 mg IM (depot injection in the buttock) given on days 1, 15, 29, and then every 4 weeks indefinitely. The effectiveness of abarelix beyond 12 months has not been established.

NOTE: Abarelix is approved with marketing restrictions. Only physicians who have enrolled in the manufacturer–sponsored prescribing program can prescribe abarelix (Plenaxis™). Call 1–866–PLENAXIS (1–866–753–6294).

IV. TOXICITY

Adverse effects associated with abarelix in men are primarily due to testosterone deprivation:

- A) Hot flashes (79%).
- B) Gynecomastia (30%).
- C) Mastalgia (31%).
- D) Insomnia (44%).
- E) QT prolongation (the QTc increased more than 30 milliseconds from baseline or the end–of–treatment QTc values were more than 450 milliseconds has been reported in 20% of 340 study patients who were on abarelix).

V. CLINICAL MONITORING

- A) Prostate–specific antigen (PSA).
- B) Serum testosterone – Abarelix should not be continued in men with persistent serum testosterone concentrations greater than 50 ng/dL, as the result likely indicates abarelix treatment failure.

ANASTROZOLE
(ARIMIDEX®)

*****FOR POSTMENOPAUSAL WOMEN ONLY*****

I. MECHANISM OF ACTION

- A) Anastrozole is a potent and selective nonsteroidal aromatase inhibitor. By selectively inhibiting aromatase, it lowers serum estradiol concentrations with no effect on the formation of adrenal corticosteroids or aldosterone. See exemestane for more details.
- B) Patients with ER-negative disease and patients who did not respond to previous tamoxifen therapy, rarely respond to anastrozole.

II. PHARMACOKINETICS

- A) Anastrozole is supplied as a 1 mg oral tablet with the usual dose being 1 mg taken once a day.
- B) Well absorbed and food does not affect the extent of absorption. Elimination is primarily via hepatic metabolism (about 85%), and to a lesser extent renal elimination (about 11%). It has a mean terminal elimination half-life of 50 hours in postmenopausal women. The major circulating metabolite of anastrozole, diazole, lacks pharmacologic activity.
- C) No dosage changes are recommended in patients with mild-to-moderate hepatic impairment. Clearance of anastrozole was decreased in patients with cirrhosis due to alcohol abuse, plasma concentrations stayed in the usual range seen in patients without liver disease. No dosage changes are necessary for patients with renal impairment.

III. DOSAGE AND ADMINISTRATION: administered orally. Available as 1 mg tablets. Dose is 1 mg PO QD. No dosage adjustments are required for renal or moderate hepatic impairment. This drug has not been studied in severe hepatic impairment so patients should be monitored closely.

IV. TOXICITY

- A) Anastrozole is well tolerated. In two trials comparing anastrozole to megestrol acetate the adverse event that was more common with anastrozole was diarrhea.
- B) Others: asthenia, nausea, headache, hot flushes, decreased bone density and pain.

BICALUTAMIDE **(CASODEX®)**

I. MECHANISM OF ACTION

- A) Binds to the receptor for dihydrotestosterone and prevents the latter from binding and entering the nucleus. More selective for peripheral androgen receptors than central receptors which is different from flutamide which binds nonselectively to both.
- B) Usually used in conjunction with leuprolide or goserelin to provide another means to offset the effects of testosterone but is effective against prostate cancer when used alone.

II. PHARMACOKINETICS

- A) Given orally but the bioavailability is unknown.
- B) Undergoes extensive metabolism to inactive metabolites that are eliminated in the urine and feces.
- C) The long half-life (6 days) allows once daily dosing which is an advantage over flutamide (given TID).
- D) Plasma protein binding 96%.

III. DOSAGE AND ADMINISTRATION:

When used in combination with a LHRH analog, the dose of bicalutamide is 50 mg PO QD. When used as monotherapy for the treatment of early-stage non-metastatic prostate cancer the dose is 50 – 150 mg PO QD. Available as a 50 mg tablet. No dosage adjustment is required in renal impairment. Bicalutamide should not be used in patients with jaundice or elevated ALT.

IV. TOXICITY

Hot flashes (9–49%); Dyspnea (7%); Impotence (5%); Gynecomastia (5%); Diarrhea (6%); Hypertension (5%).

V. CLINICAL MONITORING: LFT's; PSA.

ESTRAMUSTINE (EMCYT[®])

I. MECHANISM OF ACTION

- A) Oral, nitrogen mustard antineoplastic agent that is a combination of an estradiol molecule linked to nornitrogen mustard.
- B) Classified as an alkylating agent, but its mechanism of action is probably due to antimicrotubule activity. It binds to high molecular weight microtubule associated proteins and/or tubulin which results in the microtubule disassembly and arrest of cell division in the G₂/M phase of the cell cycle; causes rapid and dose-related DNA strand breaks.
- C) Causes a marked decrease in plasma testosterone and an increase in estrogen levels

II. PHARMACOKINETICS

- A) Elimination half-life is 20 hours.
- B) Oral bioavailability is 75%.
- C) Estramustine phosphate is readily dephosphorylated during absorption, and peak plasma concentrations are achieved in 2—3 hours. During absorption, estramustine phosphate is dephosphorylated. The main metabolites are estramustine, the estrone analog, estradiol, and estrone.
- D) Estramustine is excreted as metabolites of both the alkylating and estrogenic moieties in the bile, urine and feces. Nonrenal excretion is considered the main route of elimination.

III. DOSAGE AND ADMINISTRATION

- A) Estramustine should be swallowed with water on an empty. Do not administer with milk, milk products, or calcium-containing foods or drugs. Dairy products and calcium-rich foods or drugs may inhibit absorption of estramustine.
- B) Store under refrigeration. The capsules may be stored outside of the refrigerator at normal room temperature, out of direct sunlight, for no more than 2 days without affecting the strength of the medicine.

IV. TOXICITY

- A) Nausea/vomiting (16%/1%) are common and are considered the dose-limiting toxicities of estramustine therapy. Nausea/vomiting are usually transient and responsive to conventional antiemetics; however, intractable vomiting is occasionally noted after 6 to 8 weeks of treatment and may require the termination of therapy.
- B) Diarrhea may occur in as many as 15—30% of patients.
- C) Myelosuppression during estramustine therapy is uncommon, but leukopenia (4%) and thrombocytopenia (1%) were reported during the initial clinical trial.
- D) Decreased libido decrease, impotence, and gynecomastia.
- E) Due to its estrogen-like activity, estramustine has been associated with sodium and fluid retention, resulting in peripheral edema (20%), dyspnea (12%), mild weight gain or symptoms of congestive heart failure (3%), and cardiac decompensation (58%). About 50% of cardiac decompensation occurs within the first 2 months of therapy and 85% occur within the first year.
- F) There is an increased incidence of thrombosis/thromboembolism in men who receive this drug for prostate cancer.

EXEMESTANE
(AROMASIN®)

***** POST-MENOPAUSAL WOMEN ONLY*****

I. MECHANISM OF ACTION

- A) Aromatase is the principle enzyme that converts androgens to estrogens in pre- and postmenopausal women. In postmenopausal women the primary source of circulating estrogens is from conversion of adrenal and ovarian androgens to estrogens by the aromatase enzyme in the peripheral tissues. Estrogen deprivation through aromatase inhibition is an effective and selective treatment for some patients with hormone-dependent breast cancer.
- B) Exemestane is an irreversible, steroidal aromatase inactivator, structurally related to the natural substrate androstenedione. It acts as a false substrate for the aromatase enzyme and is processed to an intermediate that binds irreversibly to the active site of the enzyme causing its inactivation. It significantly lowers circulating estrogen concentrations but has no effect on adrenal biosynthesis of corticosteroids or aldosterone.

II. PHARMACOKINETICS

- A) Exemestane is supplied as a 25mg tablet with the usual dose being 25mg once daily after a meal.
- B) Rapidly absorbed with a mean terminal half-life of about 24 hours. It is distributed extensively into the tissues and is 90% bound to plasma proteins. It undergoes extensive metabolism with the metabolites being inactive or inhibiting aromatase with less potency compared with the parent drug. Exemestane is metabolized by cytochrome P-450 3A4.

III. DOSAGE AND ADMINISTRATION:

25 mg PO QD after a meal. If co-prescribing with a CYP 3A4 inducer, increase the dose to 50 mg PO QD.

IV. TOXICITY

- A) Exemestane is well tolerated.
- B) Body as a whole – increased sweating, fatigue, hot flashes, pain, influenza-like symptoms, edema.
- C) Cardiovascular – hypertension.
- D) Nervous – depression, insomnia, anxiety, dizziness, headache.
- E) GI – nausea, vomiting.
- F) Respiratory – dyspnea, coughing.
- G) Endocrine – decreased bone mineral density.

FLUTAMIDE **(EULEXIN[®])**

I. MECHANISM OF ACTION

- A) Binds to the receptor for dihydrotestosterone and prevents the latter from binding and entering the nucleus.
- B) Usually used in conjunction with leuprolide or goserelin to provide another means to offset the effects of testosterone but is effective against prostate cancer when used alone.

II. PHARMACOKINETICS

- A) Given orally but the bioavailability is unknown.
- B) Undergoes extensive metabolism and has an active metabolite hydroxyflutamide.
- C) Most of the metabolites are eliminated in the urine.
- D) Plasma protein binding of flutamide and hydroxyflutamide is 86–94%.

III. DOSAGE AND ADMINISTRATION:

Available as 125 mg capsules. For dosing see prostate cancer regimen section. No dosage adjustment is required for renal impairment.

IV. TOXICITY

Hot flashes (60%); Loss of libido (36%); Impotence (33%); Diarrhea (12%). The diarrhea may be due to lactose intolerance since each tablet contains 360 mg of lactose.

FULVESTRANT (FASLODEX®)

I. MECHANISM OF ACTION

A 7- α alkylamide estrogen analogue is a pure antiestrogen, which competes with endogenous estrogen for estrogen receptor binding. The relative binding affinity of fulvestrant is 89% that of estradiol while tamoxifen is 2.5%. Fulvestrant also lacks estrogen agonist activity. There is evidence that fulvestrant is not cross-resistant with tamoxifen.

II. PHARMACOKINETICS

- A) Absorption – Fulvestrant exhibits poor bioavailability; an improved oral dosage formulation is under development by Astra-Zeneca.
- B) Distribution– 99% protein (mainly LDL, VLDL and HDL) bound.
- C) Metabolism– extent unknown in liver; appears to include oxidation, hydroxylation, conjugation with glucuronic acid and/or sulphate.
- D) Elimination– elimination half-life is 40 days; less than 1% excreted renally; 99% excreted via hepatobiliary route.

III. DOSAGE AND ADMINISTRATION

Should be administered as an IM injection of 250 mg once monthly. It should be administered slowly into the buttocks as a single 5 mL injection or 2 concurrent 2.5 mL injections. Available as a 50 mg/mL solution for injection.

IV. TOXICITY

- A) Hematologic– anemia (4.5%); thromboembolic events (<1%); leukopenia (< 1%).
- B) Cardiovascular– vasodilatation (17.7%).
- C) CNS– asthenia (22.7%), headache (15.4%), dizziness (6.9%), insomnia (6.9%), paresthesia (6.4%), depression (5.7%), anxiety (5.0%), and vertigo (less than 1%).
- D) Endocrine– hot flashes (19–24%).
- E) Metabolic– peripheral edema (9%); weight gain (1–2%).
- F) Gastrointestinal– nausea (26%), vomiting (13%), constipation (12%), diarrhea (12%), abdominal pain (12%), and anorexia (9%).
- G) Genitourinary– vaginal bleeding (< 1%); the bleeding occurred mainly during the first 6 weeks after changing from existing hormonal therapy to fulvestrant therapy.
- H) Musculoskeletal– bone pain (16%), back pain (14%), arthritis (3%), and myalgia (less than 1%).
- I) Dermatologic– injection site pain (11%), rash (7%), and sweating (5%).

V. CLINICAL MONITORING

- A) Menopausal symptoms are the most difficult adverse effect to control. Considerable emotional support and pharmacologic treatment of hot flashes.
- B) Routine GYN exams are necessary to check for endometrial cancer. Monitor for vaginal bleeding.

GOSERELIN (ZOLADEX[®])

I. MECHANISM OF ACTION

- A) Testosterone or estrogen production by the testis or ovaries is regulated by the pituitary and hypothalamus.
- B) The hypothalamus produces luteinizing hormone releasing hormone (LHRH) in a pulsatile fashion. This hormone stimulates the pituitary to produce luteinizing hormone (LH). LH then is released to stimulate the testis or ovaries to produce testosterone or estrogen, respectively.
- C) Goserelin is chemically similar to LHRH but it provides continuous stimulation of the pituitary. The result is downregulation of the LHRH receptor and D/C of LH production.
- D) Prostate cancer is usually dependent upon testosterone to grow and develop. Breast cancer is often dependent upon estrogen. Giving goserelin to patients with prostate cancer or breast cancer, the tumor is deprived of an important growth factor.
- E) Goserelin causes a medical castration. Castration levels of testosterone and estrogen can be expected within 1–2 weeks.

II. PHARMACOKINETICS

- A) Peak concentrations of goserelin appear within 12–15 days for the monthly injection but within 24 hr for the 3-month injection.
- B) Plasma protein binding is less than 30%.
- C) Goserelin is metabolized as well as eliminated through the urine. No dosage adjustment is necessary for hepatic or renal dysfunction.

III. DOSAGE AND ADMINISTRATION

- A) Goserelin is administered subcutaneously into body fat.
- B) Goserelin is a polymer pellet that releases the drug slowly over 1 or 3 month period.
- C) The monthly injection is 3.6 mg and the 3-month injection is 10.8 mg.
- D) No dosage adjustment required for hepatic or renal dysfunction.

IV. TOXICITY

- A) Most common adverse effect in men is hot flashes (50%).
- B) Upon initiation of therapy, many patients, especially with bony metastasis, experience pain from a flare reaction. Goserelin causes an initial increase in LH release that causes a surge in testosterone release that causes growth of the tumor. Occurs in about 17% of patients. Use a direct anti-androgen (i.e., flutamide/casodex) during this phase.
- C) Peripheral edema in 8% of patients.
- D) Thrombophlebitis (1%).
- E) Dizziness or headache (10%).
- F) Gynecomastia (3%) and impotence (2%) in men. ↓ libido in 9% of patients. Amenorrhea in all premenopausal women Rx'd goserelin for >10 weeks.

V. CLINICAL MONITORING

- A) Initial tumor flare pain may be severe. Use of a direct anti-androgen and analgesics are recommended.
- B) Because this product comes in different strengths, be sure to verify that the correct product is used with the prescribed dosing interval.

LETROZOLE
(FEMARA®)

***** FOR USE IN POST-MENOPAUSAL WOMEN ONLY*****

I. MECHANISM OF ACTION

- A) Letrozole is nonsteroidal, type II aromatase inhibitor which competitively binds to the heme of the cytochrome P450 subunit of aromatase, the enzyme that catalyzes the final step in estrogen production.
- B) The formation of adrenal corticosteroids, aldosterone, or thyroid hormones is not affected by letrozole; only serum estradiol concentrations are affected by letrozole.
- C) In postmenopausal women, the principal source of circulating estrogens is from the conversion of adrenal and ovarian androgens (androstenedione and testosterone) to estrogens (estrone and estradiol) by aromatase in peripheral tissues.

II. PHARMACOKINETICS

- A) Absorption- well absorbed.
- B) Distribution- weakly protein bound with large volume of distribution.
- C) Metabolism- in liver; metabolized by CYP3A4 and CYP2A6; inhibits CYP2A6 and CYP2C19
- D) Elimination- half-life 2 to 4 days; 84 % renally excreted as inactive metabolites and only 6% excreted as unchanged letrozole in urine.

III. DOSAGE AND ADMINISTRATION

- A) Letrozole may be administered without regard to meals.
- B) Available as tablets of 2.5 mg usually given once daily.

IV. TOXICITY

- A) Letrozole is well tolerated.
- B) May increase LDL and total cholesterol, increase in bone resorption.

V. CLINICAL MONITORING

Consider baseline bone mineral density and lipid profile.
Periodic CBC, LFTs.

LEUPROLIDE

(ELIGARD[®]; LUPON[®], LUPRON DEPOT[®], LUPRON DEPOT-PED[®], VIADUR[™])

I. MECHANISM OF ACTION

- A) Testosterone or estrogen production by the testis or ovaries is regulated by the pituitary and hypothalamus.
- B) The hypothalamus produces luteinizing hormone releasing hormone (LHRH) in a pulsatile fashion. This hormone stimulates the pituitary to produce luteinizing hormone (LH). LH then is released to stimulate the testis or ovaries to produce testosterone or estrogen, respectively.
- C) Leuprolide is chemically similar to LHRH but it provides continuous stimulation of the pituitary. The result is down regulation of the LHRH receptor and discontinuation of LH production.
- D) Prostate cancer is usually very dependent upon testosterone to grow and develop. Breast cancer is often dependent upon estrogen. By giving leuprolide to patients with prostate cancer or breast cancer, the tumor is deprived of an important growth factor.
- E) Leuprolide causes a medical castration. Castration levels of testosterone and estrogen can be expected within 1–2 weeks.

II. PHARMACOKINETICS

- A) The bioavailability of the SC form is 94%.
- B) It distributes well to the pineal gland, pituitary gland, liver, and kidney.
- C) Plasma protein binding is 49%.
- D) Leuprolide is metabolized in the anterior pituitary and hypothalamus.

III. DOSAGE AND ADMINISTRATION

Leuprolide is available as: implant (Viadur[™]) 65mg leuprolide; Injection (Lupron[®]) 5mg/mL 2.8 mL. Also available as a powder for injections as: Depot 7.5mg (Eligard[®] Atrigel[®] Depot); Lupron Depot[®] 3.75 mg and 7.5 mg; Lupron Depot[®]–3 month: 11.25 mg and 22.5 mg; Lupron-Depot[®] –4 month: 30 mg; Lupron Depot-Ped[®]: 7.5 mg, 11.25 mg, and 15 mg.

IV. TOXICITY

- A) Most common adverse effect in men is hot flashes (50%).
- B) Upon initiation of therapy, many patients, especially with bony metastasis, experience pain from a flare reaction. Leuprolide causes an initial increase in LH release that causes a surge in testosterone release that causes growth of the tumor. Occurs in about 10% of patients. Use a direct anti-androgen (flutamide/casodex) during this phase.
- C) Peripheral edema in 8% of patients.
- D) Thrombophlebitis (1%).
- E) Dizziness or headache (10%).
- F) Gynecomastia (3%) and impotence (2%) in men. Amenorrhea in all premenopausal women who receive leuprolide for more than 10 weeks.

V. CLINICAL MONITORING

- A) Initial tumor flare pain may be severe. Use of a direct anti-androgen and analgesics are recommended.
- B) Because this product comes in different strengths, be sure to verify that the correct product is used with the prescribed dosing interval.

MEGESTROL ACETATE (MEGACE®)

I. MECHANISM OF ACTION

- A) Megestrol is a synthetic progestin with antiestrogenic properties which disrupt the estrogen receptor cycles; it interferes with the normal estrogen cycle and results in a lower LH titer.
- B) Megestrol may also have a direct effect on the endometrium. It promotes the differentiation and maintenance of endometrial tissue.
- C) Megestrol is thought to have an antiluteinizing effect that is mediated via the pituitary, resulting in a negative effect on cancerous tissues of the breast and endometrium.
- D) Megestrol enhances estrogen metabolism, which suppresses estrogen-dependent effects by decreasing plasma estrogen concentrations.
- E) Megestrol is considered 3rd/4th line therapy for breast cancer. It is less effective than tamoxifen, and its efficacy is comparable to that of aminoglutethimide.

II. PHARMACOKINETICS

- A) Megestrol is well absorbed and is taken orally.
- B) Megestrol is completely hepatically metabolized to free steroids and glucuronide conjugates.
- C) The onset of action is delayed, and is not seen until the patient has received at least 2 months therapy.
- D) Megestrol undergoes primarily renal elimination (as steroid metabolites and inactive compound); the elimination half-life is 15 - 20 hours.

III. DOSING

- A) Megestrol is supplied in 20 mg and 40 mg tablets or as a 40 mg/mL oral suspension.
- B) The dose of megestrol in the treatment of breast cancer is 160 mg/day, usually in divided doses (i.e. 40 mg PO QID).
- C) The dose used in the treatment of endometrial cancer is 40 - 320 mg/day in divided doses, although doses as high as 800 mg/day have been used.
- D) The dose in metastatic renal cell cancer is 40 mg PO QID.
- E) The dose used in prostate cancer is 40 mg PO BID - QID; a gradual loss of efficacy may occur.
- F) The dose used for the treatment of hot flashes is 20 mg PO BID.
- G) Dose to increase appetite (i.e. for anorexia) is 200 - 800 mg/day.

IV. TOXICITY

- A) Endocrine and metabolic - breakthrough bleeding/amenorrhea, menstrual changes, breast tenderness, HPA axis suppression, adrenal insufficiency, Cushing's syndrome.
- B) General - diaphoresis, edema.
- C) Skin - rash with or without pruritis, alopecia.
- D) GI - weight gain (not related to edema or fluid retention), diarrhea, and flatulence.
- E) Infrequent - hepatotoxicity, cholestatic jaundice, hepatomegaly, thrombophlebitis, weakness.

V. CLINICAL MONITORING

- A) Observe for signs of thromboembolic phenomena.
- B) Megestrol use may result in changes in thyroid and liver function tests (drug-test interaction).

MEDROXYPROGESTERONE ACETATE

(PROVERA®)

I. MECHANISM OF ACTION

- A) Medroxyprogesterone acetate (MPA) is a synthetic progestin, and is approximately 15 times more potent than progesterone.
- B) MPA inhibits the secretion of pituitary gonadotropins, which prevents follicular maturation and ovulation.
- C) MPA also stimulates the growth of mammary tissue.
- D) The exact MOA of MPA against some cancers has not been determined.

II. PHARMACOKINETICS

- A) MPA is 90% protein-bound, primarily to albumin.
- B) Oral MPA is metabolized via hydroxylation and conjugation.
- C) Once peak concentrations are achieved with the IM injection, serum concentrations begin to decrease exponentially to undetectable levels at 120 – 200 days following the injection.
- D) The metabolism of MPA to inactive metabolites may be increased twofold by aminoglutethimide.
- E) Oral MPA is eliminated in the urine and feces; elimination half-life is 38-46 hours.
- F) The elimination half-life of IM MPA is 50 days.
- G) MPA doses may need to be reduced in patients with alcoholic cirrhosis.

III. DOSING AND ADMINISTRATION

- A) MPA is available orally (2.5, 5, and 10 mg tablets) or as an IM injection (150 mg/mL: 1 mL, 400 mg/mL: 1 ml, 2.5 mL, and 10 mL).
- B) Dosing:
 - Amenorrhea: 5 – 10 mg/day for 5 – 10 days, or 2.5 mg daily.
 - Uterine bleeding: 5 – 10 mg/day for 5 – 10 days starting day 16 or 21 of each cycle.
 - Endometrial or renal cancer: 400 – 1000 mg IM Q week.
 - Breast or prostate cancer: up to 1500 mg/day for induction therapy has been used, with maintenance doses of 500 mg 1 to 3 times weekly.

IV. TOXICITY

- A) GI – nausea, weight gain/loss, anorexia, cholestatic jaundice.
- B) Endocrine – menstrual changes, gynecomastia, breast tenderness, hot flashes.
- C) Skin – rash, melasma or chloasma.
- D) Other – fluid retention, flare reaction at initiation of therapy (prostate cancer), pulmonary embolism, fatigue, weakness, impotence, local injection site reactions.

V. CLINICAL MONITORING

- A) Monitor closely for loss of vision, sudden onset of proptosis, diplopia, migraine.
- B) Monitor closely for signs of thromboembolic phenomena.

NILUTAMIDE **(NILANDRON®)**

I. MECHANISM OF ACTION

- A) Binds to the receptor for dihydrotestosterone and prevents the latter from binding and entering the nucleus.
- B) Usually used in conjunction with leuprolide or goserelin to provide another means to offset the effects of testosterone but is effective against prostate cancer when used alone.

II. PHARMACOKINETICS

- A) Given orally but the bioavailability is unknown.
- B) Undergoes extensive metabolism and has 2 active metabolites.
- C) Most of the metabolites (62% of a dose) are eliminated in the urine.

III. DOSAGE AND ADMINISTRATION:

In the management of metastatic prostate cancer the dose is 300mg PO QD for 30 days, followed by 150 mg PO QD thereafter. Available as 150 mg tablets.

IV. TOXICITY

Hot flashes (28%); Constipation (7%); Dizziness (7%); Elevated transaminases (8%); Hypertension (5%); Nausea (10%); Ethanol intolerance (5%).

TAMOXIFEN (NOLVADEX®; SOLTOMOX™; TAMOXIFEN)

I. MECHANISM OF ACTION

- A) In the treatment of breast cancer, tamoxifen is an estrogen antagonist that reversibly binds to the estrogen receptor on the surface of breast cancer cells.
- B) Estrogen mediated cell growth is impaired. Progesterone receptor induction is blocked.
- C) The tamoxifen/estrogen receptor complex can bind to DNA but transcription of RNA is impaired.
- D) Tamoxifen activity is cell cycle specific for the G₂ phase. Its activity is cytostatic.
- E) In other tissues, tamoxifen is pro-estrogenic such as in the uterus (causing endometrial cancer) and the bone (reducing osteoporosis risk). It also lowers the risk of coronary artery disease by lowering low density lipoprotein concentrations.

II. PHARMACOKINETICS

- A) Tamoxifen is available as an oral tablet and the usual dose is 10 mg twice daily or 20 mg once daily.
- B) The absolute bioavailability is unknown but approximately 75% of a dose is recovered in the stool as conjugates of tamoxifen.
- C) Tamoxifen is extensively bound to plasma proteins. Its CSF concentrations are negligible. The liver and uterus accumulate the greatest concentrations of tamoxifen
- D) Tamoxifen is metabolized in the liver via the cytochrome P450 CYP2D6 enzyme to antiestrogenic active metabolites, which are subsequently eliminated in the stool. The half-life is between 3 and 21 days. There is enterohepatic recirculation. Obstructive liver disease can cause accumulation of tamoxifen and its metabolites but specific dosing adjustment guidelines are not available.

III. DOSAGE AND ADMINISTRATION: See Breast Cancer Section.

IV. TOXICITY

- A) Marrow suppression is rare.
- B) Premenopausal women can experience menopausal symptoms such as hot flashes and nausea. Although various remedies have been tried no truly effective remedy exists and patients should be given a trial of agents such as a SSRI or venlafaxine (Effexor) or clonidine. Overall about 66% of women taking tamoxifen will have menopausal symptoms.
- C) Premenopausal women are also initially at risk of pregnancy because tamoxifen induces ovulation. Tamoxifen may have teratogenic effects on the fetus of pregnant women.
- D) Endometrial carcinoma-Routine age appropriate GYN exams are necessary while on tamoxifen. The risk of breast cancer recurrence without tamoxifen far outweighs the risk of endometrial cancer. Monitor for vaginal bleeding.
- E) Dermatologic-skin rashes, pruritus.
- F) Flare reaction- Patients may experience increased pain in bony metastasis or soft tissue sites. The reaction fades with time. Hypocalcaemia may also occur.
- G) Retinopathy -Occurs with very high doses (> 200 mg/day) but not at standard doses for breast cancer. Patients at increased risk for cataract development.
- H) Thromboembolic disorders-Tamoxifen does suppress antithrombin III plasma concentrations but the risk of pulmonary emboli or DVT is small for most women.

V. CLINICAL MONITORING

- A) Tamoxifen is well tolerated and very effective.
- B) Menopausal symptoms are the most difficult adverse effect to control. Considerable emotional support and trial and error approaches to hot flashes control are the best therapies.
- C) Routine age appropriate GYN exams are necessary to check for endometrial cancer. Monitor for vaginal bleeding.
- D) Periodic ophthalmic examinations to monitor for cataract development.
- E) Select populations of patients (i.e., rapid metabolizers via CYP2D6) may be tested for potential effectiveness of Tamoxifen [Reference: [Goetz MP, et al. *Breast Cancer Res Treat* 2006 Nov 18; Epub ahead of print](#)].

TOREMIFENE (FARESTON®)

I. MECHANISM OF ACTION

- A) Toremifene is a nonsteroidal antiestrogen. It is a triphenylethylene derivative of tamoxifen.
- B) It competitively binds to estrogen receptors on tumors and other tissue targets, producing a nuclear complex that decreases DNA synthesis and inhibits estrogen effects.
- C) Cells accumulate in G₀ and G₁ phases.
- D) Toremifene is cytostatic.
- E) Its efficacy in breast cancer is equivalent to that of tamoxifen, and cross-resistance may be seen.

II. PHARMACOKINETICS

- A) Well-absorbed.
- B) Extensive protein binding (>99.5%).
- C) Undergoes extensive hepatic metabolism, primarily by CYP3A4 to N-demethyltoremifene, which is also antiestrogenic but has weak *in vivo* antitumor potency. Toremifene undergoes enterohepatic circulation.
- D) The elimination half-life of toremifene is 5 hours, and that of its principal active metabolite, N-demethyltoremifene, is 6 hours.
- E) Dose adjustments may be indicated for patients with liver disease.
- F) Mostly fecal elimination. 10% of the drug is recovered in the urine during a 1-week period.

III. DOSAGE AND ADMINISTRATION:

Oral tablet; usual dose is 60 mg PO once daily.

IV. TOXICITY

- A) Side effects seen with toremifene are nearly identical to those seen with Tamoxifen.
- B) Premenopausal women may experience menopausal symptoms such as nausea and hot flashes.
- C) Thromboembolism – women taking toremifene are at an increased risk of developing venous thrombosis, pulmonary embolism, or arterial thrombosis.
- D) Ocular – visual acuity changes, cataract development, or retinopathy may occur while on toremifene therapy.
- E) Tumor flare can occur in the first weeks of toremifene therapy.
- F) Although endometrial or uterine cancer has not been linked with toremifene therapy, it is possible that toremifene therapy carries the same risk as tamoxifen therapy.