Temsirilimus (Torisel)

**Manufacturer:** Wyeth Pharmaceuticals, Philadelphia, PA

**Indication:** Temsirolimus is indicated for the treatment of advanced renal cell carcinoma.

**Drug Class:** As an inhibitor of the mammalian target of rapamycin kinase (mTOR), temsirolimus is considered to be an antineoplastic agent.

**Uniqueness of Drug:** Temsirolimus is the only marketed cancer therapy that specifically inhibits mTOR kinase, a key protein in cells that regulates cell proliferation, cell growth, and cell survival. Temsirolimus binds to an intracellular protein, and the protein–drug complex inhibits the mTOR activity that controls cell division. Inhibition of mTOR activity resulted in arrested growth of treated tumor cells in phase G1. Clinically, temsirolimus resulted in prolonged overall survival in patients with renal cell carcinoma.

**Warnings and Precautions:**

**Hypersensitivity Reactions.** Hypersensitivity reactions may include anaphylaxis, dyspnea, flushing, and chest pain. Temsirolimus should be used with caution in patients with known hypersensitivity to temsirolimus, its metabolites (including sirolimus), polysorbate 80, or any of its other components. An H₁-receptor antagonist should be administered to patients before the start of the intravenous (IV) temsirolimus infusion. Temsirolimus should be used with caution in patients with known hypersensitivity to antihistamines or in patients who cannot receive antihistamines for other reasons.

If a hypersensitivity reaction occurs during the infusion, the infusion should be stopped and the patient should be observed for at least 30 to 60 minutes. At the discretion of the physician, treatment may be resumed with the administration of an H₁-receptor antagonist such as diphenhydramine (Benadryl, McNeil/Johnson & Johnson), if not previously administered, or with an H₂-receptor antagonist such as IV famotidine 20 mg (Pepcid, Merck) or IV ranitidine 50 mg (Zantac, GlaxoSmithKline) approximately 30 minutes before the infusion is restarted. The infusion may then be resumed at a slower rate (up to 60 minutes).

**Hyperglycemia/Glucose Intolerance.** Temsirolimus is likely to result in increased serum glucose levels. In the phase 3 trial, 89% of patients had at least one elevated serum glucose value during treatment, and 26% of patients reported hyperglycemia as an adverse event. This effect may signal the need for an increased or initial dose of insulin or oral hypoglycemic agent therapy. Glucose levels should be tested before and during treatment. Patients should be advised to report excessive thirst or any increase in the volume or frequency of urination.

**Infections.** Temsirolimus may result in immunosuppression. Patients should be carefully observed for the occurrence of infections, including opportunistic infections.

**Interstitial Lung Disease.** Cases of interstitial lung disease, some resulting in death, occurred in patients who received temsirolimus. Some patients were asymptomatic, and infiltrates were detected on computed tomography (CT) scans or chest radiographs. Others presented with dyspnea, cough, hypoxia, and fever. Some patients need to discontinue temsirolimus or treatment with corticosteroids or antibiotics, and some patients continued treatment without additional intervention. Patients should be advised to promptly report any new or worsening respiratory symptoms.

**Hyperlipemia.** The use of temsirolimus is likely to result in elevated serum triglyceride and cholesterol levels. In the phase 3 trial, 87% of patients had at least one elevated cholesterol value and 83% had at least one elevated triglyceride value. In this case, an increased or initial dose of lipid-lowering agents might be required. Serum cholesterol and triglyceride levels should be tested before and during treatment with temsirolimus.

**Bowel Perforation.** Cases of fatal bowel perforation have occurred. Patients presented with fever, abdominal pain, metabolic acidosis, bloody stools, diarrhea, or acute abdomen. Patients should be advised to report any new or worsening abdominal pain or blood in the stool.

**Renal Failure.** Cases of rapidly progressive and sometimes fatal acute renal failure, not clearly related to disease progression, occurred in patients who received temsirolimus. Some of these patients were not responsive to dialysis.

**Wound Healing Complications.** Temsirolimus has been associated with abnormal wound healing. Therefore, caution should be exercised with the use of this product in the perioperative period.

**Intracerebral Hemorrhage.** Patients with central nervous system (CNS) tumors or patients who are receiving anticoagulation therapy may be at an increased risk for intracerebral bleeding while receiving temsirolimus.

**Coadministration with Inducers or Inhibitors of CYP 3A4 metabolism:**

**Agents inducing CYP 3A4 metabolism.** Strong inducers of CYP 3A4 and CYP 3A5 such as dexamethasone (Decadron, Merck), carbamazepine (Tegetrol, Novartis), phenytoin (Dilantin, Pfizer), phenobarbital, rifampin, rifabutin (Mycobutin, Pfizer), and rifampicin may decrease exposure of the active metabolite, sirolimus. If alternative treatment cannot be given, a dose adjustment should be considered. St. John’s Wort may unpredictably decrease temsirolimus plasma concentrations; therefore, patients receiving temsirolimus should not take St. John’s Wort concomitantly.

**Agents inhibiting CYP3A4 metabolism.** Strong CYP3A4 inhibitors such as atazanavir (Reyataz, Bristol-Myers Squibb), clarithromycin (Biaxin, Abbott), indinavir (Crixivan, Merck), itraconazole (Sporanox, PriCara), ketoconazole (Nizoral, PriCara), nefazodone (Serzone, Bristol-Myers Squibb), nelfinavir (Viracept, GlaxoSmithKline), ritonavir (Norvir, Pfizer), and saquinavir (Invirase, Bristol-Myers Squibb) may unexpectedly increase temsirolimus plasma concentrations; therefore, patients receiving temsirolimus should not take these drugs concomitantly.

The author is President of Pharmaceutical and Scientific Services at Marvin M. Goldenberg, LLC, in Westfield, New Jersey. His e-mail address is mmgpotter@comcast.com.
temsirolimus. Continue contraception for three months after the last dose of throughout treatment. It is recommended that the couple contraception of childbearing age should use reliable contraception partners of childbearing age should be notified of the potential hazard to the fetus. in pregnancy or if a patient becomes pregnant while taking this drug, administered to pregnant women. If it is used during pregnancy throughout temsirolimus treatment and for three months after therapy ends. Temsirolimus can cause fetal harm when exposed to the fetus and sperm before starting treatment. she should be apprised of the potential hazard to the fetus. in rats, intrauterine and embryofetal adverse effects were observed with a dose of 2.7 mg/m² per day. In rabbits, the intrauterine and embryofetal adverse effects were observed at the oral dose of 7.2 mg/m² or more per day. Women of childbearing age should avoid becoming pregnant through temsirolimus treatment and for three months after therapy ends. Temsirolimus can cause fetal harm when administered to pregnant women. If it is used during pregnancy or if a patient becomes pregnant while taking this drug, she should be apprised of the potential hazard to the fetus. Men should be counseled about the effects of temsirolimus on the fetus and sperm before starting treatment. Men with partners of childbearing age should use reliable contraception throughout treatment. It is recommended that the couple continue contraception for three months after the last dose of temsirolimus.

Dosage and Administration:
Advanced Renal Cell Carcinoma. The recommended temsirolimus dose is 25 mg infused over 30 to 60 minutes once a week. Treatment should continue until disease progression or unacceptable toxicity occurs.

Premedication. Patients should receive prophylactic IV diphenhydramine 25 to 50 mg or a similar antihistamine approximately 30 minutes before the start of each dose of temsirolimus.

Dosage Interruption or Adjustment. Temsirolimus should be delayed if the absolute neutrophil count is below 1,000/mm³; if the platelet count is below 75,000/mm³; or if grade 3 or greater adverse reactions occur. After toxicities have resolved to grade 2 or less, temsirolimus may be restarted with the dose reduced by 5 mg/week to a dose no lower than 15 mg/week.

Dose Modification Guidelines:
Concomitant strong CYP3A4 inhibitors. The concomitant use of strong CYP 3A4 inhibitors should be avoided (e.g. ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, saquinavir, telithromycin, voriconazole [Vfend, Pfizer]). Grapefruit juice may also increase plasma concentrations of sirolimus and should be avoided. If patients must take a strong CYP 3A4 inhibitor, a temsirolimus dose reduction to 12.5 mg/week should be considered. It is predicted that this dose of temsirolimus will adjust the area under-the-curve (AUC) concentration to the range observed without inhibitors; however, there are no clinical data with this dose adjustment in patients receiving strong CYP 3A4 inhibitors. If the strong inhibitor is discontinued, a washout period of approximately one week should be allowed before the temsirolimus dose is adjusted back to the dose that was used before initiation of the strong CYP 3A4 inhibitor.

Concomitant strong CYP 3A4 inducers. The use of concomitant strong CYP 3A4 inducers should be avoided (e.g. dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, ritampicin, phenobarbital). If patients must take a strong CYP3A4 inducer, a temsirolimus dose increase from 25 mg/week up to 50 mg/week should be considered. This dose of temsirolimus is predicted to adjust the AUC to the range observed without inducers. However, there are no clinical data with this dose adjustment in patients receiving strong CYP 3A4 inducers. If the strong inducer is discontinued, the temsirolimus dose that was used before the strong CYP 3A4 inducer was initiated should be resumed.

Commentary: Renal cell carcinoma accounts for approximately 8% of kidney cancers. The American Cancer Society estimated that 51,190 new cases of kidney cancer would be diagnosed in 2007. More than 40% of these patients have advanced disease when they are initially seen. Temsirolimus is the only cancer therapy that specifically inhibits mTOR kinase, a cellular protein that regulates cell proliferation, cell growth, and cell survival.

Advanced renal cell carcinoma is very difficult to treat. Developing effective treatments for this stage of disease is a major challenge. Temsirolimus is the first drug to demonstrate a significant increase in overall survival for patients with the most aggressive form of kidney cancer, and it is considered a needed option for treatment. The approval of temsirolimus reinforces the potential of mTOR inhibition as a new approach in oncology.

The product’s safety information indicates the possibility of hypersensitivity reactions, elevated blood glucose levels, immunosuppression, interstitial lung disease, and bowel perforation. One caveat of the FDA approval is a postmarketing commitment whereby the company has agreed to submit two completed study reports and data sets: one for QT prolongation and an ongoing report on hepatic impairment.

Sources: www.pharmacyonesource.com; www.wyeth.com

Estradiol Gel 0.1% (Divigel)
Manufacturer: Upsher-Smith Laboratories, Inc., Maple Grove, MN
Indication: Estradiol gel 0.1% is indicated for the treatment of moderate-to-severe hot flashes associated with menopause.
Drug Class: The clear, colorless topical gel is odorless when dry. It is designed to deliver sustained circulating concentrations of estradiol when applied once daily to the skin. The gel is applied to a small area (200 cm²) of the thigh in a thin, quick-drying layer. The active component of the gel is estradiol, chemically defined as estra-1,3,5(10)-triene-3,17β-diol.

Uniqueness of Product: Estradiol, the major estrogenic hormone secreted by the human ovary, is delivered to the systemic circulation after topical application. The gel offers the lowest approved dose of estradiol available for women with menopausal vasomotor symptoms.

Boxed Warning: Estrogens increase the risk of endometrial cancer. Close clinical surveillance of all women taking estrogens is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. There is no evidence that the use of “natural” estrogens results in a different endometrial risk profile than synthetic estrogens at equivalent estrogen doses.

Cardiovascular and Other Risks. Estrogens with or without progestins should not be used to prevent cardiovascular disease or dementia. The estrogen-alone substudy of the Women’s Health Initiative (WHI) reported increased risks of stroke and deep vein thrombosis (DVT) in postmenopausal women 50 to 79 years of age during 6.8 years and 7.1 years, respectively, who used oral conjugated estrogens 0.625 mg alone per day, compared with placebo. Conjugated estrogens are derived from the urine of pregnant mares.

The estrogen-plus-progestin substudy of the WHI reported an increased risk of myocardial infarction (MI), stroke, invasive breast cancer, pulmonary emboli, and DVT in postmenopausal women during 5.6 years of treatment with oral conjugated estrogens 0.625 mg combined with medroxyprogesterone acetate (MPA) 2.5 mg/day, compared with placebo.

The Women’s Health Initiative Memory Study (WHIMS), a substudy of the WHI, reported an increased risk of probable dementia in postmenopausal women 65 years of age or older during 5.2 years of treatment with conjugated estrogens 0.625 mg alone and during four years of taking conjugated estrogens 0.625 mg plus MPA 2.5 mg, compared with placebo. It is unknown whether this finding applies to younger postmenopausal women.

Other doses of oral conjugated estrogens with MPA and other combinations and dosage forms of estrogens and progestins were not studied in the WHI clinical trials. In the absence of comparable data, these risks should be assumed to be similar. Because of these risks, estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration.

Warnings: Cardiovascular Disorders. Estrogen-alone therapy has been associated with an increased risk of stroke and DVT. Estrogen-plus-progestin therapy is associated with an increased risk of MI as well as stroke, venous thrombosis, and pulmonary embolism. If any of these occur or are suspected, estrogens should be discontinued immediately. Risk factors for arterial vascular disease (e.g., hypertension, diabetes mellitus, tobacco use, hypercholesterolemia, and obesity) or venous thromboembolism (VTE) (e.g., a personal history or family history of VTE, obesity, and systemic lupus erythematosus) should be managed appropriately.

Stroke. In the estrogen-alone substudy, a statistically significant increased risk of stroke was observed with conjugated estrogens 0.625 mg daily (44 per 10,000 women-years), compared with placebo (32 per 10,000 women-years). The increased risk was observed in the first year and persisted.

In the estrogen-plus-progestin substudy, a statistically significant increased risk of stroke was reported with the same regimen, compared with placebo (31 vs. 24 per 10,000 women-years). The increase in risk was noted after the first year and persisted.

Coronary Heart Disease. In the estrogen-alone substudy, no overall effect on coronary heart disease (CHD) events (nonfatal MI, silent MI, or death from CHD) was reported in women receiving estrogen alone compared with those receiving placebo.

In the estrogen-plus-progestin substudy, no statistically significant increase of CHD events was reported with conjugated estrogens plus MPA, compared with placebo (39 vs. 33 per 10,000 women-years). An increase in relative risk was demonstrated in the first year and a trend of decreasing relative risk was reported in years two through five.

In 2,763 postmenopausal women with documented heart disease (average age, 66.7 years), the Heart and Estrogen/Progestin Replacement Study (HERS) demonstrated no cardiovascular benefit after treatment with conjugated estrogens 0.625 mg/day plus MPA 2.5 mg/day.

During an average follow-up of 4.1 years, this treatment did not reduce the overall rate of CHD events in postmenopausal women with established CHD. There were more CHD events in the hormone-treated group than in the placebo group in the first year but not during the subsequent years. In an open-label extension of the original HERS trial (HERS II), 2,321 women agreed to participate. Average follow-up in HERS II was an additional 2.7 years, for a total of 6.8 years overall. Rates of CHD events were comparable between the hormone and placebo groups in HERS, HERS II, and overall.

In a large prospective clinical trial in men, large doses of conjugated estrogens at 5 mg/day, comparable to doses used to treat cancer of the prostate and breast, increased the risks of nonfatal MI, pulmonary embolism, and thrombophlebitis.

Venous Thromboembolism. In the estrogen-alone substudy, the risk of VTE (DVT and pulmonary embolism), was increased for women taking conjugated estrogens compared with those receiving placebo (30 vs. 22 per 10,000 women-years), although only the increased risk of DVT reached statistical significance (23 vs. 15 per 10,000 women-years). The increased risk of VTE was demonstrated during the first two years.

In the estrogen-plus-progestin substudy, a statistically significant two-fold greater rate of VTE was reported for conjugated estrogens plus MPA compared with placebo (35 vs. 17 per 10,000 women-years). Statistically significant increases in risk for both DVT (26 vs. 13 per 10,000 women-years) and pulmonary embolism (18 vs. 8 per 10,000 women-years) were also noted. The increased VTE risk occurred during the first year and persisted.
If feasible, estrogens should be discontinued at least four to six weeks before surgery of the type that can be associated with an increased risk of thromboembolism or during periods of prolonged immobilization.

**Endometrial Cancer.** The use of unopposed estrogens in women with an intact uterus has been associated with an increased risk of endometrial cancer. The reported endometrial cancer risk among women taking unopposed estrogen is about two to 12 times greater than in non-users, and it appears dependent on the duration of treatment and on the estrogen dose. Most studies show no significant increased risk associated with the use of estrogens for less than one year. The greatest risk is associated with prolonged use for five to 10 years or more (a 15-fold to 24-fold increased risk). This risk can persist for at least eight to 15 years after estrogen therapy is discontinued.

Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. There is no evidence that natural estrogens have a different endometrial risk profile than synthetic estrogens of equivalent estrogen dose. Adding a progestin to estrogen therapy can reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer.

**Breast Cancer.** In some studies, the use of estrogens and progestins by postmenopausal women has been reported to increase the risk of breast cancer. The most important randomized clinical trial providing information about this occurrence is the WHI. The results from observational studies are generally consistent with those of the WHI trial.

Observational studies have also reported an increased risk of breast cancer with estrogen-plus-progestin combination therapy and a smaller increased risk for estrogen-alone therapy after several years of use. For both findings, the excess risk increased with duration of use and appeared to return to the baseline risk over about five years after stopping treatment; only the observational studies have substantial data on risk after stopping. In these studies, the risk of breast cancer was greater and became apparent earlier with estrogen plus progestin, compared with estrogen alone. However, these studies have not found a significant variation in the risk of breast cancer associated with different estrogens or different estrogen-plus-progestin combinations, doses, or routes of administration.

In the estrogen-alone substudy, after an average of 7.1 years of follow-up, conjugated estrogens at doses of 0.625 mg daily were not associated with an increased risk of invasive breast cancer (risk ratio [RR], 0.80; 95% confidence interval [CI], 0.62–1.04).

In the estrogen-plus-progestin substudy, after a mean follow-up of 5.6 years, the WHI substudy reported an increased risk of breast cancer. In this substudy, prior use of estrogen alone or estrogen/progestin combination hormone therapy was reported by 26% of the women. The RR of invasive breast cancer was 1.24 (95% CI, 1.01–1.54); the absolute risk with estrogen plus progestin was 41 cases per 10,000 women-years compared with 33 for placebo.

Among women who reported previous use of hormone therapy, the RR of invasive breast cancer was 1.86. The absolute risk was 46 cases per 10,000 women-years for estrogen plus progestin, compared with 25 for placebo.

Among women who reported no prior use of hormone therapy, the RR of invasive breast cancer was 1.09. The absolute risk was 40 cases per 10,000 women-years for estrogen plus progestin, compared with 36 for placebo.

In the WHI trial, invasive breast cancers were larger and were diagnosed at a more advanced stage with estrogen plus progestin, compared with placebo. Metastatic disease was rare, with no apparent difference between the two groups. Other prognostic factors such as histologic subtype, grade, and hormone receptor status did not differ between the groups.

The use of estrogen alone and estrogen plus progestin has been reported to result in an increased number of abnormal mammograms necessitating further evaluation.

**Dementia.** In the estrogen-alone WHIMS substudy, 2,947 women 65 to 79 years of age who had undergone hysterectomy were randomly assigned to receive conjugated estrogens 0.625 mg daily or placebo.

In the estrogen-plus-progestin WHIMS substudy, 4,532 postmenopausal women 65 to 79 years of age received conjugated estrogens plus MPA 0.625 mg/2.5 mg daily or placebo.

In the estrogen-alone substudy, after an average follow-up of 5.2 years, probable dementia was diagnosed in 28 women using estrogen alone and in 19 women receiving placebo. The RR of probable dementia for conjugated estrogens alone versus placebo was 1.49 (95% CI, 0.83–2.66). The absolute risk of probable dementia for conjugated estrogens alone was 37 cases per 10,000 women-years, compared with 25 for placebo.

In the estrogen-plus-progestin substudy, after an average follow-up of four years, probable dementia was diagnosed in 40 women taking estrogen plus progestin and in 21 women taking placebo. The RR of probable dementia for estrogen-plus-progestin versus placebo was 2.05 (95% CI, 1.21–3.48). The absolute risk of probable dementia for conjugated estrogens plus MPA was 45 cases per 10,000 women-years, compared with 22 for placebo.

When data from the two populations were pooled as planned in the WHIMS protocol, the reported overall relative risk for probable dementia was 1.76 (95% CI, 1.19–2.60). Because both substudies were conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women.

**Gallbladder Disease.** A two-fold to four-fold increase in the risk of gallbladder disease requiring surgery has been reported in postmenopausal women receiving estrogens.

**Hypercalcemia.** Estrogens can lead to severe hypercalcemia in patients with breast cancer and bone metastases. If hypercalcemia occurs, estrogens should be stopped and appropriate measures should be taken to reduce serum calcium levels.

**Visual Abnormalities.** Retinal vascular thrombosis has been reported in patients receiving estrogens. Medication should be discontinued pending examination if the patient experiences a sudden partial or complete loss of vision or a sudden onset of proptosis, diplopia, or migraine. If the examination reveals papilledema or retinal vascular lesions, estrogens should be permanently discontinued.
Pharmaceutical Approval Update

**Precautions:**

*Addition of a Progestin (in Women without a Hysterectomy).* Studies of the addition of a progestin for 10 or more days of a cycle of estrogen administration, or daily with estrogen in a continuous regimen, have reported a lowered incidence of endometrial hyperplasia than would be induced by estrogen treatment alone. Endometrial hyperplasia may be a precursor to endometrial cancer; however, risks may be associated with the use of progestins with estrogens, compared with estrogen-alone regimens. These include a possible increased risk of breast cancer, adverse effects on lipoprotein metabolism (lower high-density lipoprotein levels and elevated low-density lipoprotein levels), and impaired glucose tolerance.

**Hypertension.** In a small number of case reports, substantial increases in blood pressure have been attributed to idiosyncratic reactions to estrogens. Although a large, randomized, placebo-controlled clinical trial showed no generalized effect of estrogens on blood pressure, blood pressure should be monitored at regular intervals with estrogen use.

**Hypertriglyceridemia.** In patients with pre-existing hypertriglyceridemia, estrogen therapy has been associated with elevated plasma triglyceride levels, leading to pancreatitis and other complications.

**Impaired Liver Function and History of Cholestatic Jaundice.** Estrogens may be poorly metabolized in patients with impaired liver function. For patients with a history of cholestatic jaundice associated with prior estrogen use or with pregnancy, caution should be exercised. In the case of recurrence, estrogens should be discontinued.

**Hypothyroidism.** Estrogen leads to increased thyroid-binding globulin (TBG) levels. Patients with normal thyroid function can compensate for the increased TBG by making more thyroid hormone, thus maintaining free thyroxine and triiodothyronine serum concentrations in the normal range. Patients dependent on thyroid hormone replacement who are also receiving estrogens may require increased doses of thyroid hormone. Monitoring of thyroid function is recommended for these patients to maintain acceptable free thyroid hormone levels.

**Fluid Retention.** Estrogens may cause some degree of fluid retention. Because of this, patients who have conditions that might be influenced by this factor (cardiac or renal dysfunction) warrant careful observation when estrogens are prescribed.

**Hypocalcemia.** Estrogens should be used with caution in individuals with severe hypocalcemia.

**Ovarian Cancer.** In the estrogen-plus-progestin substudy of the WHI, after an average follow-up of 5.6 years, the RR for ovarian cancer for this regimen, compared with placebo, was 1.58 (95% nCI, 0.77–3.24) but was not statistically significant. The absolute risk for estrogen-plus-progestin therapy was 4.2 cases per 10,000 women-years and 2.7 for placebo. In some studies, estrogen-only products, especially for 10 or more years, were associated with an increased risk of ovarian cancer. Other epidemiological studies have not found these associations.

**Exacerbation of Endometriosis.** Endometriosis may be exacerbated with estrogen administration. Malignant transformations of residual endometrial implants have been reported in women treated with estrogen alone after hysterectomy. For patients with residual post-hysterectomy endometriosis, the addition of progestin should be considered.

**Exacerbation of Other Conditions.** Estrogens may cause an exacerbation of asthma, diabetes mellitus, epilepsy, migraine or porphyria, systemic lupus erythematosus, and hepatic hemangiomas. Estrogens should be used with caution in women with these conditions.

**Photosensitivity and Photoallergy.** The effects of direct sun exposure to estradiol gel 0.1% application sites have not been evaluated in clinical trials. Nonclinical studies in guinea pigs showed no phototoxicity or photosensitivity. The gel absorbs light primarily at wavelengths below 290 nm and is not considered to have photosensitizing potential.

**Sunscreens.** Studies of other topical estrogen gel products have shown that sunscreens have the potential for changing the systemic exposure of topically applied estrogen gels. The effect of applying sunscreen plus estradiol gel 0.1% to the same site has not been clinically evaluated.

**Alcohol-Based Gels.** Gels with an alcohol base are flammable. Patients should avoid fire, flame, or smoking until the gel has dried. Occluding the area where the topical drug product is applied with clothing or other barriers is not recommended until the gel is completely dried.

**Potential for Estradiol Transfer.** There is a potential for the drug to be transferred from one individual to another following physical contact of application sites. In a study that evaluated transferability to males from their female contacts, estradiol levels were somewhat elevated over baseline values in the males, but the degree of transferability was inconclusive. Patients are advised to avoid skin contact with other people until the gel is completely dried. The site should be covered with clothing after drying.

**Effects of Washing.** Washing the application site with soap and water one hour after gel application resulted in a 30% to 38% decrease in the mean total 24-hour exposure to estradiol. Patients should refrain from washing the application site for at least one hour after the gel is applied.

**Dosage and Administration:**

Topical estradiol gel 0.1% is available in strengths of 0.25, 0.5, and 1.0 g/day. Each gram of the gel product contains 1 mg of estradiol. The usual initial dose is 0.25 g daily. Dosage adjustments may vary according to individual patient response. Health care providers should periodically reassess the dose.

The gel should be applied once daily on the skin of either the right or left upper thigh. The application surface area should be about 5 by 7 inches (the size of two palm prints). The entire contents of a unit dose packet should be applied each day. To avoid potential skin irritation, patients should apply the gel to the right or left upper thigh on alternating days. They should not apply the gel to the face, breasts, or irritated skin or in or around the vagina. After the gel is applied, it should be allowed to dry. The application site should not be washed within one hour after application. Patients should avoid contact of the gel with the eyes, and they should wash their hands after applying the gel.

When estrogen is prescribed for postmenopausal women with a uterus, a progestin should also be given to reduce the risk of endometrial cancer. Women without a uterus do not
need progestin. The use of estrogen, alone or with a progestin, should be with the lowest effective dose and for the shortest duration. Patients should be re-evaluated periodically as appropriate (at three-month to six-month intervals) to determine whether treatment is still necessary.

For women with a uterus, endometrial sampling should be undertaken to rule out malignancy if there is undiagnosed persistent or recurring abnormal vaginal bleeding.

**Commentary:** The most common menopause-related discomfort is a vasomotor symptom commonly called hot flashes (or flushes). Although the exact cause is unclear, they are thought to be the result of changes in the hypothalamus, which regulates the body’s temperature. If the hypothalamus mistakenly senses that a woman is too warm, it starts a chain of events to cool her down. Blood vessels near the surface of the skin begin to dilate, increasing blood flow to the surface in an attempt to dissipate body heat. This produces a red, flushed look to the face and neck in light-skinned women. Women may also perspire to cool the body down. An increased pulse rate and a sensation of rapid heartbeat may also occur. Hot flashes are often followed by a cold chill; some women experience only the chill.

The best treatment depends on how severe the symptoms are, how much they interfere with quality of life, the woman’s personal preferences, and her health profile. If treatment is needed, hot flashes can usually be reduced or eliminated with lifestyle changes or nonprescription or prescription therapies. Some older oral estrogen therapies contain conjugated estrogens. Now that estradiol gel 0.1% is available, systemic estrogen therapy might not be necessary.

In clinical trials with estradiol gel 1%, women experienced a low incidence of adverse events and a decrease in the frequency and severity of hot flashes as early as two weeks from the start of therapy. This product provides the lowest approved dose of estradiol therapy on the market to treat hot flashes, although a boxed warning is associated with the gel.

**Sources:** http://divigelus.com; www.menopause.org

---

**Somatropin (Recombinant DNA origin) Injection (Norditropin)**

**Manufacturer:** Novo Nordisk, Princeton, NJ

**Indications:**

**Pediatric Patients:** Norditropin is indicated for the long-term treatment of children with growth failure due to inadequate secretion of endogenous growth hormone (GH). GH is also known as somatotropin.

**Adult Patients:** Norditropin injection cartridges (somatropin) can replace endogenous GH in adults with GH deficiency who meet either of these criteria:

**Adult onset:** Patients with GH deficiency, either alone or associated with multiple hormone deficiencies (hypopituitarism), as a result of pituitary disease, hypothalamic disease, surgery, radiation therapy, or trauma.

**Childhood onset:** Patients who were deficient in GH during childhood as a result of congenital, genetic, acquired, or idiopathic causes. The confirmation of the diagnosis of adult GH deficiency in both groups usually requires an appropriate GH stimulation test. However, confirmatory GH stimulation testing may not be necessary in patients with congenital or genetic GH deficiency or multiple pituitary hormone deficiencies resulting from organic disease.

**Drug Class:** Somatropin is a polypeptide hormone of recombinant DNA (rDNA) origin that stimulates growth in humans. The hormone is synthesized by a special strain of *Escherichia coli* bacteria that has been modified by the addition of a plasmid that carries the gene for human GH. Somatropin of rDNA origin contains the identical sequence of 191 amino acids constituting the naturally occurring pituitary human GH. The molecular weight is about 22,000 daltons.

**Uniqueness of Drug:** If a child’s short stature is caused by a deficiency of human GH, the child might benefit from GH therapy. Children who have GH deficiency may be able to achieve their full growth potential with daily injections of GH.

**Pediatric Patients:** Norditropin injection cartridges (somatropin) can replace endogenous GH in children as a result of congenital, genetic, acquired, or idiopathic causes. The confirmation of the diagnosis of adult GH deficiency in both groups usually requires an appropriate GH stimulation test. However, confirmatory GH stimulation testing may not be necessary in patients with congenital or genetic GH deficiency or multiple pituitary hormone deficiencies resulting from organic disease.

**Drug Class:** Somatropin is a polypeptide hormone of recombinant DNA (rDNA) origin that stimulates growth in humans. The hormone is synthesized by a special strain of *Escherichia coli* bacteria that has been modified by the addition of a plasmid that carries the gene for human GH. Somatropin of rDNA origin contains the identical sequence of 191 amino acids constituting the naturally occurring pituitary human GH. The molecular weight is about 22,000 daltons.
mellitus may be unmasked during treatment. Glucose levels should be monitored periodically in all patients, especially in those with risk factors for diabetes mellitus, such as obesity (including obese patients with Prader-Willi syndrome), Turner syndrome, or a family history of diabetes mellitus.

Patients with pre-existing type-1 or type-2 diabetes mellitus or impaired glucose tolerance should be monitored closely during somatropin therapy. The doses of insulin or oral antihyperglycemic agents may need to be adjusted when somatropin therapy is instituted in these patients.

Patients with pre-existing tumors or GH deficiency secondary to an intracranial lesion should be examined routinely for progression or recurrence of the underlying disease process. In children, the literature has not shown a relationship between somatropin replacement therapy and CNS tumor recurrence or new extracranial tumors. However, in childhood cancer survivors, an increased risk of a second neoplasm has been reported in patients receiving somatropin after their first neoplasm. Intracranial tumors, especially meningiomas in patients receiving radiation to the head for their first neoplasm, were the most common of these second neoplasms. In adults, it is unknown whether there is any relationship between somatropin therapy and CNS tumor recurrence.

Intracranial hypertension (IH) with papilledema, visual changes, headache, nausea, or vomiting has been reported in a small number of patients. Symptoms usually occurred within the first eight weeks after the initiation of somatropin therapy. In all cases, IH-associated signs and symptoms rapidly resolved after cessation of therapy or after a reduction of the somatropin dose.

Funduscopic examination should be performed routinely before treatment with somatropin begins to exclude pre-existing papilledema and, periodically, during the course of somatropin therapy. If papilledema is observed by funduscopy during treatment, somatropin should be stopped. If somatropin-induced IH is diagnosed, somatropin can be restarted at a lower dose after IH-associated signs and symptoms have resolved. Patients with Turner syndrome, chronic renal insufficiency, and Prader-Willi syndrome may be at increased risk for IH.

In patients with hypopituitarism (multiple hormone deficiencies), standard hormonal replacement should be monitored closely when somatropin is administered. Undiagnosed or untreated hypothyroidism may prevent an optimal response to somatropin, especially the growth response in children.

Patients with Turner syndrome have an inherently increased risk for autoimmune thyroid disease and primary hypothyroidism. In patients with GH deficiency, central (secondary) hypothyroidism may first become evident or worsen during somatropin treatment. Therefore, patients should have periodic thyroid function tests, and thyroid hormone replacement therapy should be initiated or adjusted when indicated.

Patients should be monitored carefully for any malignant transformation of skin lesions. When subcutaneous (SQ) somatropin is administered at the same site over a long period of time, tissue atrophy may result. This can be avoided if the physician uses alternative injection sites.

As with any protein product, local or systemic allergic reactions may occur. Parents and patients should be informed that such reactions are possible and that they should seek prompt medical attention if a reaction occurs.

**Pediatric Patients.** A slipped capital femoral epiphysis may occur more frequently in patients with endocrine disorders (including pediatric GH deficiency and Turner syndrome) or in patients undergoing rapid growth. Children with an onset of a limp or a complaint of hip or knee pain during somatropin therapy should be evaluated.

Progression of scoliosis can occur in patients who experience rapid growth. Because somatropin increases the growth rate, patients with a history of scoliosis who are receiving somatropin should be monitored for the progression of scoliosis. However, somatropin has not been shown to increase the occurrence of scoliosis. Skeletal abnormalities, including scoliosis, are commonly seen in untreated patients with Turner syndrome. Scoliosis is also common in untreated patients with Prader-Willi syndrome. Physicians should be alert to these abnormalities, which may become manifested during somatropin therapy.

**Adults.** Patients with epiphyseal closure who were treated with somatropin in childhood should be re-evaluated according to the criteria in the indications before continuing somatropin therapy at the reduced dose level recommended for GH-deficient adults. Fluid retention may occur during somatropin replacement in adults. Clinical manifestations of fluid retention are usually transient and dose-dependent. Experience with prolonged treatment in adults is limited.

**Dosage and Administration:**

**Pediatric Patients.** The dosage and schedule of administration of somatropin must be tailored for each patient. For the treatment of GH insufficiency in children, a dose of 0.024 to 0.034 mg/kg per day of body weight, six to seven times a week, by SQ injection is recommended. The thigh is the preferred site of injection, but the injection site should be rotated.

Somatropin treatment of growth failure resulting from GH deficiency should be discontinued when the epiphyses are fused. Patients who do not respond adequately during somatropin therapy should be evaluated to determine the cause of unresponsiveness.

**Adults.** The recommended dosage at the start of therapy is not more than 0.004 mg/kg given as a daily SQ injection. The dosage may be increased to no more than 0.016 mg/kg per day after approximately six weeks according to individual patient requirements.

Clinical response, side effects, and determination of age-adjusted and sex-adjusted serum insulin growth factor-I (IGF-I) levels may be used to guide dose titration. Alternatively, according to the more recent literature, a starting dose of approximately 0.2 mg/day (from 0.15 to 0.30 mg/day) may be used without regard to body weight. This dose can be increased gradually every one to two months by increments of approximately 0.1 to 0.2 mg/day, according to individual requirements based on clinical responses and serum IGF-I concentrations. During therapy, the somatropin dose should be decreased if required by the occurrence of adverse events or serum IGF-I levels above the age and sex-specific normal range.

Maintenance dosages vary considerably. A lower starting dose and smaller dose increments should be considered for...
older patients, who are more prone to the adverse effects of somatropin than younger patients. Obese patients are also more likely to experience adverse effects when treated with a weight-based regimen. To reach defined treatment goals, estrogen-replete women may need higher doses than men. Oral estrogen administration may increase the dose requirements in women.

**All Patients.** The injection cartridges are administered via the NordiPen injection pen. Each cartridge size has a color-coded corresponding pen that is graduated to deliver the appropriate dose based on the concentration of somatropin in the cartridge. Somatropin must not be injected if the solution is cloudy or if it contains particulate matter. The solution should be used only if it is clear and colorless.

**Commentary:** The newest FDA indication for somatropin is for short stature in children with Noonan syndrome. When the pituitary gland does not produce or release enough GH, a deficiency results. In children, GH is a primary regulator of growth. In adults, GH helps regulate metabolism and helps keep bones and muscles healthy.

Noonan syndrome is a rare autosomal dominant genetic syndrome commonly characterized by short stature, congenital heart defects, and unique facial features. Patients can have widely set or down-slanting eyes and a webbed neck. Congenital heart disease occurs in half of affected patients. Up to 80% of children with Noonan syndrome have significant short stature. Few treatment options are available to help their physical development, and the approval of the drug marks an exciting advance for children with this rare condition. Somatropin injection has received an orphan drug designation.

**Sources:** www.norditropin-us.com; www.news-medical.net; www.magicfoundation.org