

## Drug Adverse Reactions/Side Effects as per Product Information Leaflets/Patient Information Sites Oct 2011.

### 1. Prolia (Denosumab)

Source: [http://pi.amgen.com/united\\_states/prolia/prolia\\_pi.pdf](http://pi.amgen.com/united_states/prolia/prolia_pi.pdf)

**Hypocalcemia:** Must be corrected before initiating Prolia. May worsen, especially in patients with renal impairment. Adequately supplement patients with calcium and vitamin D. Hypocalcemia may be exacerbated by the use of Prolia. In patients predisposed to hypocalcemia and disturbances of mineral metabolism (e.g. history of hypoparathyroidism, thyroid surgery, parathyroid surgery, malabsorption syndromes, excision of small intestine, severe renal impairment [creatinine clearance (CrCL) < 30 mL/min] or receiving dialysis), clinical monitoring of calcium and mineral levels (phosphorus and magnesium) is highly recommended.

Hypocalcemia following Prolia administration is a significant risk in patients with severe renal impairment [CrCL < 30 mL/min], or receiving dialysis. Instruct all patients with severe renal impairment, including those receiving dialysis, about the symptoms of hypocalcemia and the importance of maintaining calcium levels with adequate calcium and vitamin D supplementation.

**Dermatologic reactions:** Dermatitis, rashes, and eczema have been reported.

Consider discontinuing Prolia if severe symptoms develop

**Serious infections including skin infections:** May occur, including those leading to hospitalization. Serious skin infections, as well as infections of the abdomen, urinary tract, and ear, were more frequent in patients treated with Prolia. Endocarditis was also reported more frequently in Prolia-treated subjects. Advise patients to seek prompt medical attention if they develop signs or symptoms of infection, including cellulitis.

**Osteonecrosis of the jaw:** Has been reported with Prolia. Monitor for symptoms.

**Suppression of bone turnover:** Significant suppression has been demonstrated. In clinical trials in women with postmenopausal osteoporosis, treatment with Prolia resulted in significant suppression of bone remodeling as evidenced by markers of bone turnover and bone histomorphometry. The significance of these findings and the effect of long-term treatment with Prolia are unknown. The long-term consequences of the degree of suppression of bone remodeling observed with Prolia may contribute to adverse outcomes such as osteonecrosis of the jaw, atypical fractures, and delayed fracture healing. Monitor patients for these consequences.

## ADVERSE REACTIONS

Postmenopausal osteoporosis: Most common adverse reactions (> 5% and more common than placebo) were: back pain, pain in extremity, hypercholesterolemia, musculoskeletal pain, and cystitis. Pancreatitis has been reported in clinical trials.

Bone loss due to hormone ablation for cancer: Most common adverse reactions ( $\geq$  10% and more common than placebo) were: arthralgia and back pain. Pain in extremity and musculoskeletal pain have also been reported in clinical trials.

The most common adverse reactions leading to discontinuation of Prolia are back pain and constipation.

## USE IN SPECIFIC POPULATIONS

*Pregnancy:* Based on animal data, may cause foetal harm. Pregnancy Surveillance Program available.

*Nursing mothers:* May impair mammary gland development and lactation. Discontinue drug when nursing

*Paediatric patients:* Safety and efficacy not established.

*Renal impairment:* No dose adjustment is necessary in patients with renal impairment. Patients with creatinine clearance < 30 mL/min or receiving dialysis are at risk for hypocalcemia. Supplement with calcium and vitamin D, and consider monitoring serum calcium.

## 1. Bisphosphonates

Under review - Due for publication 1<sup>st</sup> November 2011.

## 2. Forsteo (PTH)

Source: <http://www.medicines.ie/medicine/8818/PIL/Forsteo/>

### POSSIBLE SIDE EFFECTS

The most common side effects (affects more than 1 user in 10) are:

- pain in limb

Common side effects (1 to 10 users in 100) are:	Uncommon side effects (affects 1 to 10 users in 1000) are:
<ul style="list-style-type: none"><li>• feeling sick</li><li>• headache</li><li>• dizziness</li><li>• increase in blood cholesterol levels</li><li>• depression</li><li>• neuralgic pain in the leg</li><li>• feeling faint</li><li>• irregular heart beats</li><li>• breathlessness</li><li>• increased sweating</li><li>• muscle cramps</li><li>• loss of energy</li><li>• tiredness</li><li>• chest pain</li><li>• low blood pressure</li><li>• heartburn (painful or burning sensation just below the breast bone)</li><li>• low haemoglobin or red blood cell count (anaemia)</li></ul>	<ul style="list-style-type: none"><li>• increased heart rate</li><li>• shortness of breath</li><li>• haemorrhoids (piles)</li><li>• accidental loss or leakage of urine</li><li>• increased need to pass water</li><li>• weight increase</li><li>• kidney stones</li></ul>

Other uncommon side effects reported include pain in the muscles and pain in the joints.

Some people may experience discomfort such as redness of the skin, pain, swelling, itching, bruising or minor bleeding around the area of the injection. This should clear up in a few days or weeks.

Cases of fainting have been reported in association with teriparatide use.

Some patients treated with FORSTEO have had an increase in their blood calcium level (Hypercalcaemia).

Rare side effects (affects 1 to 10 users in 10,000): Some patients have experienced allergic reactions soon after injection, consisting of breathlessness, swelling of the face, rash and chest pain.

Cases of reduced kidney function, including renal failure have been reported in association with Teriparatide. Other rare side effects include swelling, mainly in the hands, feet and legs.

Some patients have experienced severe back cramps or pain, which led to hospitalisation.

FORSTEO may also cause an increase in an enzyme called alkaline phosphatase

### 3. Evista/ Raloxifene (SERMS)

Source: <http://pi.lilly.com/us/evista-ppi.pdf>

Serious and life-threatening side effects can occur while taking EVISTA. These include blood clots and dying from stroke:

- Increased risk of blood clots in the legs (deep vein thrombosis) and lungs (pulmonary embolism) have been reported with EVISTA. Women who have or have had blood clots in the legs, lungs, or eyes should not take EVISTA.
- Women who have had a heart attack or are at risk for a heart attack may have an increased risk of dying from stroke when taking EVISTA.

The most common side effects of EVISTA are hot flashes, leg cramps, swelling of the feet, ankles, and legs, flu syndrome, joint pain, and sweating. Hot flashes are more common during the first 6 months after starting treatment.

Source: <http://www.drugs.com/sfx/raloxifene-side-effects.html>

General:	General side effects have included infection (11% to 15%), flu syndrome (15%), and abdominal pain (7%). The most common general side effects were hot flashes (25%) and leg cramps (6%). Hot flashes or flushes tended to occur during the first six months of therapy.
Cardiovascular	<p>Raloxifene should be discontinued at least 72 hours prior to and during periods of immobilization. Therapy should be resumed only after the patient is fully ambulatory. Patients should be advised to avoid prolonged restrictions of movement during travel. The use of raloxifene in women predisposed to thromboembolic disease, such as women with congestive heart failure and malignancy, should be carefully considered.</p> <p>A large (7,705 women), 3.3 year study reported raloxifene was associated with an increased risk for venous thromboembolism (relative risk 2.1, 95% confidence interval 1.2-3.8)</p> <p>Cardiovascular side effects have included decreased fibrinogen 12% (versus 2% with estrogen) and Plasminogen Activator Inhibitor-1 2% (versus 9% with estrogen). However, analysis of clinical study data revealed an increased risk of venous thromboembolic events, such as deep vein thrombosis, pulmonary embolism, and retinal vein thrombosis associated with use of raloxifene. The greatest risk of these events occurs within the first four months of treatment.</p> <p>Chest pain occurred in 4% of raloxifene treated patients.</p>
Genitourinary:	Genitourinary side effects have included vaginal bleeding (6% versus HRT 64%), vaginitis (4%), UTI (4%), cystitis (3%), leukorrhea (3%), endometrial disorder (uterine-related) (3%), and breast pain (4% versus HRT 38%).

	Endometrial proliferation or an increased risk of breast cancer has not been reported with raloxifene.
Dermatologic:	Dermatologic side effects have included rash (6%) and sweating (3%).
Gastrointestinal:	Gastrointestinal side effects have included nausea (9%), vomiting (3%), dyspepsia (6%), flatulence (2% to 3%), GI disorder (3%), and gastroenteritis (3%).
Metabolic:	Metabolic effects of raloxifene therapy have resulted in a less positive effect on lipids than conjugated estrogen. High density lipoprotein (HDL) is increased 15% (versus 33% with estrogen). Lipoprotein (a) is decreased 7% (versus 19% with estrogen). Low density lipoprotein (LDL) is decreased 12% (versus 14% with estrogen).  Limited clinical data suggest that women with a history of marked hypertriglyceridemia (>5.6 mmol/L or >500 mg/dL) in response to treatment with oral estrogen or estrogen plus progestin may develop increased levels of triglycerides when treated with raloxifene.  Metabolic side effects have included weight gain (9%) and peripheral edema (3%).
Musculoskeletal:	Musculoskeletal side effects have included arthralgia (11%), myalgia (8%), leg cramps (6%), and arthritis (4%).
Nervous system:	Nervous system side effects have included depression (6%), insomnia (6%) and fever (3%), hot flashes (25% to 29% versus HRT 3% and placebo 18%), and migraine headaches (2%).
Respiratory:	Respiratory side effects have included sinusitis (10%), pharyngitis (8%), cough increased (6%), pneumonia (3%), and laryngitis (2%).
Ocular:	Ocular side effects have included very rare reports of retinal vein occlusion.

## 4. HRT

Source: <http://www.patient.co.uk/health/Menopause-and-HRT.htm> for full text.

**“Venous thromboembolism:** This is a blood clot that can cause a deep vein thrombosis (DVT). In some cases the clot may travel to your lung and cause a pulmonary embolism (PE). Together, DVT and PE are known as venous thromboembolism. The risk seems to be higher with combined HRT compared to oestrogen-only HRT and the risk is also higher in the

first year that you take HRT. This risk seems to be slightly lower if you use HRT patches rather than HRT tablets taken by mouth.

*In women aged 50-59 years, over a five-year period:*

- About 5 in 1,000 women who do not use HRT are likely to develop a blood clot.
- In 1,000 women taking oestrogen-only HRT for five years, there will be an extra two women who will develop a blood clot.
- In 1,000 women taking combined HRT for five years, there will be an extra seven women who will develop a blood clot.

*In women aged 60-69, over a five-year period:*

- About 8 in 1,000 women who do not use HRT are likely to develop a blood clot.
- In 1,000 women taking oestrogen-only HRT for five years, there will be an extra two women who will have a blood clot.
- In 1,000 women taking combined HRT for five years, there will be an extra 10 women who will have a blood clot.

**Breast cancer:**

Small increased risk of breast cancer. Combined (oestrogen and progesterone) HRT has a higher risk than oestrogen-only HRT. This risk increases the longer you have used HRT. When you have been off HRT for five years, you have the same risk of breast cancer as someone who has not taken HRT.

*In women aged 50-59 years:*

- About 10 per 1,000 women who do not use HRT are likely to develop breast cancer over a five year period.
- In 1,000 women who are taking oestrogen-only HRT for five years, there will be an extra two women who will develop breast cancer.
- In 1,000 women taking combined HRT for five years, there will be an extra six women who will develop breast cancer.
- About 20 per 1,000 women who do not use HRT are likely to develop breast cancer over a 10-year period.
- In 1,000 women who are taking oestrogen-only HRT for 10 years, there will be an extra six women who will develop breast cancer.
- In 1,000 women taking combined HRT for 10 years, there will be an extra 24 women who will develop breast cancer.

*In women aged 60-69 years:*

- About 15 per 1,000 women who do not use HRT are likely to develop breast cancer over a 5-year period.
- In 1,000 women who are taking oestrogen-only HRT for 5 years, there will be an extra 3 women who will develop breast cancer.
- In 1,000 women who are taking combined HRT for 5 years, there will be an extra 9 women who will develop breast cancer.
- About 30 per 1,000 women who do not use HRT are likely to develop breast cancer over a 10-year period.
- In 1,000 women who are taking oestrogen-only HRT for 10 years, there will be an extra 9 women who will develop breast cancer.
- In 1,000 women who are taking combined HRT for 10 years, there will be an extra 36 women who will develop breast cancer.

## **Stroke**

Some previous big studies, including those mentioned above, have shown that there is a small increased risk of stroke in women taking either oestrogen-only or combined HRT. They have shown that:

*In women aged 50-59 years:*

- About 4 in 1,000 women who do not take HRT will have a stroke over a 5-year period.
- In 1,000 women who take oestrogen-only HRT for five years, there will be an extra one woman per 1,000 who will have a stroke.
- In 1,000 women who take combined HRT for five years, there will be an extra one woman per 1,000 who will have a stroke.

*In women aged 60-69 years:*

- About 9 in 1,000 women who do not take HRT will have a stroke over a 5-year period.
- In 1,000 women taking oestrogen-only HRT for five years, there will be an extra 3 women per 1,000 who will have a stroke.
- In 1,000 women taking combined HRT for five years, there will be an extra 3 women per 1,000 who will have a stroke.

However, a study was published in June 2010 in the British Medical Journal (owned by the British Medical Association). It suggested that women using HRT in the form of patches containing low doses of oestrogen may not have an increased risk of stroke compared with non-HRT users. In the same study, those using HRT taken by mouth, or HRT patches with a higher dose of oestrogen (more than 50 micrograms), were shown to have an increased risk of stroke compared with non-HRT users. The increased risk of stroke with those taking HRT tablets was about the same as that shown in the previous studies mentioned above.

This was a big study that looked at over 850,000 women in the UK. However, despite the large numbers of women in the study, the number of women who actually had a stroke was small and the number of women taking HRT at the time of their stroke even smaller. Because of this, *there needs to be some caution in the interpretation of the study results because statistics become less reliable the fewer the numbers involved.* The study did take into account things that may increase a woman's risk

of stroke, for example smoking, being overweight, high blood pressure or heart disease. However, other factors may also come into play that the study could not account for. For example, whether the women using the HRT patches with low-dose oestrogen in the study may have been a group of more health-conscious women who exercised more, ate more healthily and were therefore less likely to have a stroke anyway.

Saying that, on balance, if you are considering taking HRT, this new study did show that perhaps it may be safer in terms of your risk of stroke if you use HRT patches containing low dose oestrogen rather than HRT tablets or patches containing higher doses of oestrogen.

**Coronary heart disease:**

Coronary heart disease refers to disease of the coronary (heart) arteries. It is the usual cause of angina and heart attacks. So far, studies have shown that oestrogen-only HRT does not seem to increase your risk of coronary heart disease. However, trials have shown that in women who start combined HRT more than 10 years after their menopause, there is a small increased risk of coronary heart disease. There are only a few trials that have looked at younger women who have started HRT at an earlier stage. However, some of these trials have suggested that these women have a lower risk of heart disease with HRT compared to older women and that HRT may even be protective.

**Cancer of the uterus (womb):**

There is an increased risk of cancer of the uterus due to the oestrogen part of HRT. By taking combined HRT containing oestrogen and progesterone, this risk reduces significantly (see above). This is the reason why progestogen is included in HRT. However, you should always see your doctor if you have any abnormal vaginal bleeding which develops after starting HRT. For example, heavy bleeding, irregular bleeding, or bleeding after having sex. If you have had a total hysterectomy for whatever reason, you should only need to take oestrogen-only HRT.

**Cancer of the ovary:**

There is a slightly increased risk of developing this cancer if you use oestrogen-only HRT or combined HRT. This risk decreases after you stop HRT. If either combined or oestrogen-only HRT is taken for five years or less, this increased risk is thought to be very small (there will be less than one extra woman who develops ovarian cancer per 1,000 women taking HRT). If HRT is taken for 10 years, there will be between 1-2 extra women who develop ovarian cancer per 1,000 women taking HRT.

**Dementia:**

If you start HRT after the age of 65, it is not thought to protect against dementia. Also, combined HRT may increase

the risk of dementia in women over the age of 75 years. HRT is not advised to help prevent dementia.”

Source: <http://www.ifpa.ie/eng/Media-Info/Medical-Updates/HRT> for full text

“The IMB summarised the conclusions of the review (Women’s Health Initiative Study) as follows:

**Breast cancer:** There is uncertainty regarding the increase in the incidence of breast cancer in oestrogen-only HRT users, given that low or no risk was observed in many recent studies including WHI. The WHI trial indicated that there is a lack of increase in the risk of breast cancer in users of oestrogen-only HRT compared with combined HRT.

**Endometrial cancer:** In the MWS, no risk was observed in users of combined sequential or continuous HRT.

**Ovarian cancer:** There is possibly a small increase in risk in users of combined HRT.

**Coronary artery disease:** An increase in risk is likely to be found only in combined HRT users, not in oestrogen-only HRT users. The risk increases with age.

**Stroke:** Data from the WHI trial show the same increase in risk of stroke in users of oestrogen only HRT as in users of combined HRT, which is independent of duration of use.

**Venous thromboembolism:** A contra-indication of known thrombophilic disorders has been considered necessary. There is new evidence from the WHI trial on risks associated with oestrogen-only HRT, including a lower risk of VTE compared with combined HRT.”