Pharmacological therapy is recommended for men and women with osteoporosis, including those who have experienced a fragility fracture.¹

This guide has been developed to provide an up to date overview of the medicines that are currently available for the treatment of osteoporosis, their activity, efficacy and for whom they should be prescribed.

The information provided is a summary of data about medicines for osteoporosis. Please review full Product Information and PBS listings for additional information before prescribing.

Who should be treated?

People with osteoporosis

- With a fracture
  - Initiate treatment immediately
- Without a fracture
  - Treatment is recommended when risk factors are present, but may not be necessary if modifiable risk factors only are present, or in women under 55 or men under 60 years of age.
- Women and men with secondary osteoporosis:
  - Any underlying causes of osteoporosis (eg: coeliac disease, inflammatory conditions, hyperparathyroidism/ hyperthyroidism, low testosterone, early menopause, chronic liver/kidney disease and other secondary causes) should also be treated.

People with osteopenia

- Women and men with osteopenia and a fracture:
  - Treatment is recommended for people with a vertebral fracture.
  - Treatment is generally recommended for people with a non-vertebral fracture.
- Women and men with osteopenia but no fracture:
  - There are limited data available on the efficacy of therapeutic intervention for these individuals.
  - Consider treatment for men and women aged over 65 if T-score is very low (-2.0 to -2.5) and if other risk factors are present.
  - Monitor and maintain adequate calcium intake and vitamin D levels and recommend a regular exercise program.
  - Educate regarding the signs of a spinal fracture.
  - Repeat DXA scan in 2-5 years.

People with special circumstances

- All people on corticosteroid therapy (oral or inhaled) of 7.5 mg per day for at least 3 months with a T-Score of -1.5 or less should receive drug therapy. This will have a preventative effect on bone loss and should be continued for the duration of the corticosteroid therapy.
- Women with breast cancer starting treatment with aromatase inhibitors should be assessed for their absolute fracture risk and may benefit from treatment with anti-resorptive agents.

People with normal BMD

- There is no need to treat people with normal BMD, but if they have risk factors for osteoporosis it is important to ensure an adequate calcium intake, adequate vitamin D levels and to recommend regular exercise.
- A repeat DXA could be considered in 2-5 years time to monitor bone health, depending on the risk factors.

<table>
<thead>
<tr>
<th>Summary of drug treatment</th>
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</thead>
<tbody>
<tr>
<td><strong>BMD</strong></td>
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<tr>
<td>&lt;-2.5</td>
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<tr>
<td>&lt; -2.5</td>
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<tr>
<td>-1 to -2.5</td>
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<td>-1 to -2.5</td>
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<td>&gt; -1</td>
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</tbody>
</table>
First-line treatments
Bisphosphonates such as alendronate, risedronate and zoledronic acid, and the SERM raloxifene, have each been shown to inhibit excessive bone resorption, increase BMD and reduce fracture risk by between 30% and 60%. They cannot however reverse structural damage. Newer agents such as denosumab and strontium ranelate are also effective in increasing BMD and reducing fracture risk.

Bisphosphonates

Action
- Bisphosphonates are bone-specific. They inhibit osteoclast-mediated bone resorption and allow bone mass to increase, which reduces the risk of fracture. Three bisphosphonates are currently available for treatment of osteoporosis – alendronate, risedronate, and zoledronic acid.

Efficacy
- The potent bisphosphonates alendronate, risedronate (Actonel, or generic alternatives), and zoledronic acid (Aclasta) are effective first-line options for vertebral, hip and non-vertebral fracture prevention.
- They demonstrate approximately 30-70% reduction in vertebral fractures in studies of women with one or more baseline spinal fractures and a reduction of 30-50% in hip fractures. The reduction in fracture rate is seen within 6-12 months. They have also been demonstrated to reduce bed day use and healthcare costs.

Forms
- Alendronate and risedronate are available in a variety of forms including daily tablets, weekly tablets and packaged combinations with vitamin D, or with vitamin D plus calcium. Risedronate is also available as an enteric coated tablet (marketed as Actonel EC) packaged either alone or in combination with calcium and vitamin D.
- Zoledronic acid is delivered as a once yearly, fifteen-minute intravenous infusion delivered by either a GP or Practice Nurse.

PBS listing
- The bisphosphonates alendronate, risedronate and zoledronic acid are currently subsidised by the PBS for treatment of osteoporosis once a minimal trauma fracture has occurred for people of any age. They are also on the PBS for treatment of osteoporosis in people aged 70 years and over with a BMD T-Score of less than or equal to -2.5 (alendronate, risedronate) or < -3.0 (zoledronic acid).

Supplementation
- If commencing bisphosphonates, it is important to ensure that patients have adequate vitamin D levels and an adequate calcium intake. If supplementation is required, oral vitamin D (400-800 IU) and oral calcium (500-600 mg elemental calcium daily) may be co-prescribed, or bisphosphonate products combined with vitamin D and or calcium could also be considered.

Precautions
- The bisphosphonates have poor bioavailability. The oral forms must be taken on an empty stomach, at least half an hour before or 2 hours after food (with a full glass of plain water only).
- The exception is enteric coated risedronate, which can be consumed either with or without food.
- Calcium supplements and oral bisphosphonates should be taken at least two hours apart, otherwise the absorption of the bisphosphonate can be compromised.
- After swallowing an oral bisphosphonate, the patient should remain upright for at least 30 minutes. Some patients misunderstand this to mean remaining still, however the patient can move about but should be counselled not to lie down during this 30 minute period.

Side effects associated with bisphosphonates
- The most common side effect of bisphosphonates is mild to moderate gastrointestinal discomfort.
- Rare instances of oesophagitis have been reported with oral bisphosphonates. To minimise the risk of oesophagitis, oral bisphosphonates should be avoided in people with oesophageal abnormalities, such as stricture or achalasia.
- One well publicised but rare adverse event associated with bisphosphonates is osteonecrosis of the jaw.
- This has been most commonly reported in cancer patients using intravenous bisphosphonates (zoledronic acid and pamidronate) in doses 10-20 times higher than those normally associated with oral bisphosphonates.
- Cases have also been reported in people taking oral bisphosphonates and denosumab for osteoporosis but it is rare (estimated risk of one case in 10,000 – 100,000 patient years of treatment) and these uncommon cases are milder cases than those seen in cancer patients. This problem can be precipitated by dental extractions. GPs should be aware of this rare potential side effect and be able to discuss it with their patients.
- If the patient has poor dental hygiene and may require an extraction, they should be advised to see their dentist before starting on bisphosphonates. For those already taking bisphosphonates, and a dental extraction is required, consider stopping for 3 months before and after extraction.
- Atypical fractures.
- More recently, atypical fractures have been reported after long-term use of the longest used bisphosphonate, alendronate. No causal relationship has been proven and reports have been associated with other bisphosphonates such as risedronate and zoledronate.
- The risk of atypical fractures is very low compared with the number of fractures prevented by bisphosphonate treatment, even in long-term users of these agents.
Denosumab (Prolia)
- Denosumab is a monoclonal antibody which inhibits RANK Ligand (RANKL). It is used for the prevention of spinal, non-spinal and hip fractures.
- Denosumab exhibits a different mode of action to the bisphosphonates. It works through disrupting the action of RANKL, associated with the development and survival of osteoblasts. In doing so, it reduces bone turnover.

Efficacy
- Although head to head studies have not been conducted, denosumab achieves a similar reduction in fracture rates to those of the bisphosphonates, including zoledronic acid. Research has shown that Denosumab reduces the rate of spinal fractures by 68% over three years, hip fractures by 40% and other fracture types by 20%.11

Form
- Given as a 6 monthly subcutaneous injection, this drug can be administered by the doctor, nurse, carer or by self administration.

PBS listing
- For use in people with established osteoporosis and a minimal trauma fracture or people aged 70 years or over with a T-Score of less than or equal to -2.5.
- It is not PBS listed for use in men or for patients taking corticosteroids.

Strontium ranelate (Protos)

Action
- Strontium has a dual action – increasing bone formation markers and decreasing bone resorption markers by a small amount. However, its main mode of action is uncertain.

Efficacy
- Strontium ranelate reduces vertebral fractures by 50%; non-vertebral fractures by 16%, and major fractures by 19% in women over 74 years of age with low BMD at the femoral neck.12
- The effects of strontium ranelate on bone density in men are similar to those in postmenopausal women.13

Form
- A once daily dose, taken as a powder mixed with water.

PBS listing
- For people with established osteoporosis and a minimal trauma fracture.
- It is not PBS listed for patients taking corticosteroids

Precautions
- It is best taken at bed-time, at least 2 hours after food, calcium-containing products or antacids.
- Subsequent DXA scans can give artificially high readings – radiologist will require notification.

Contraindications
- Protos is associated with an increased risk of cardiovascular events. It should only be used when other osteoporosis medications are unsuitable, and should not be used in people with past or current ischaemic heart disease, peripheral vascular disease, cerebrovascular disease, uncontrolled hypertension, venous thromboembolism or pulmonary embolism.
- Caution is advised for patients with risk factors for cardiovascular events or venous thrombosis. Patients should be informed of the risks and monitored every 6 months.

Side effects
- Possible side effects include nausea, diarrhoea, headache and skin irritation. Venous thrombosis is an uncommon side effect.
- A very rare side effect is drug hypersensitivity syndrome or drug rash with eosinophilia and systemic symptoms (DRESS). Most cases resolve after discontinuation of the drug and treatment with corticosteroid therapy.

HRT

Action
- Hormone Replacement Therapy (HRT) relieves menopausal symptoms. By restoring oestrogen levels, HRT has also been shown to slow the rate of bone loss and reduce the risk of fracture, and may be prescribed for younger women (below the age of 60) when specific anti-osteoporosis medications are not suitable, or if management of menopausal symptoms is also required.

Efficacy
- For maximum benefit in reducing bone loss, HRT should be started soon after menopause. Studies have shown that HRT, even at low doses, can significantly increase bone density14 and reduce the rate of fracture.15 On average, HRT reduces the risk of spinal and hip fractures by 40%. It is still not known how long, if at all, the protective effects of HRT on bone continue after HRT treatment ceases. For women over 60 who continue to have low bone density and who are still at risk of fracture, it is important that other treatments for osteoporosis are commenced when HRT is stopped.

Form
- Oestrogens are available as tablets, skin patches and gels. Progestins are available as tablets and skin patches.
- Patches or gels may be better for those who cannot absorb tablets.
- Patches or gels are also better for those who have high triglyceride concentrations or who are at risk of DVT (deep venous thrombosis). This includes women who are overweight and who smoke.
- Vaginal oestrogen in creams, pessaries or tablets is available for women suffering from vaginal dryness or painful intercourse.
- An alternative method is to deliver the progestogen directly into the endometrium using the levonorgestrel containing intrauterine system (Mirena).

PBS listing
- Several forms of HRT are available on the PBS.
Precautions

● The prolonged use of hormone therapy for prevention of diseases such as heart disease or stroke, is not recommended. Recent studies have shown that long-term HRT use may increase the risk of heart disease and stroke. The risks of using HRT increase with increasing age. In women below the age of 60 who do not have risk factors for breast cancer, cardiovascular disease, stroke or venous thrombosis, the risks associated with short-term HRT are very low. HRT should be considered as a short-term treatment (up to 5 years) for osteoporosis for women below the age of 60.

● Women over 60 are at higher risk of cardiovascular disease, stroke and venous thrombosis. The risks of HRT for these women may outweigh any benefits for bone health. While individual risks will vary, other treatments for osteoporosis such as bisphosphonates, denosumab, strontium or SERMs are more suitable for women over 60.

Side effects

● HRT needs to be individually tailored. Some women experience side effects during the early stages of treatment, including breakthrough bleeding, breast tenderness and bloating.

● Blood clots. The risk of developing a blood clot increases with age. Younger women face a one in 10,000 risk of blood clots, but this increases to one in 5,000 for those on oral HRT. Older women (50-60) years, face a one in 1,000 risk of blood clots, and this increases to one in 500 when on oral HRT.

Selective oestrogen receptor modulators (SERMs)

Action

● SERMs interact with oestrogen receptors, but in a different way to oestrogen, resulting in mixed agonist and antagonist effects in different body tissues.

Efficacy

● Raloxifene (Evista) increases BMD at the spine and hip, reducing the risk of vertebral fracture for women with osteopenia and osteoporosis by up to 50%, but has not been demonstrated to reduce non-vertebral/hip fractures.

Form

● Raloxifene is taken as a daily tablet.

PBS listing

● Raloxifene is listed for the use in post-menopausal women who have osteoporosis and have suffered a minimal trauma fracture.

Side effects

● Unlike HRT, raloxifene does not stimulate the endometrium and therefore is not associated with an increased frequency of vaginal bleeding or an increased risk of endometrial cancer. However, it may exacerbate vasomotor menopausal symptoms (eg: hot flushes and leg cramps).

● Raloxifene has also been demonstrated to reduce the risk of invasive breast cancer in postmenopausal women on long-term therapy (greater than 5 years), without increasing the risk of endometrial cancer. However, this may be balanced by an increased risk of VTE and fatal stroke.

● An increased risk of venous thrombosis has been reported with raloxifene, similar to that seen with HRT, so it should be stopped if people are immobilised for a prolonged period.

Tibolone (Livial)

This therapy is a different form of hormone therapy for treating menopausal symptoms. There is evidence that tibolone has beneficial effects on bone and leads to an increased bone density and fracture prevention. It may have the same risks as conventional HRT.

Second-line treatment

Teriparatide (Forteo)

Action

● Teriparatide (Forteo) a form of the anabolic agent parathyroid hormone, stimulates bone formation and hence, bone density and strength.

Efficacy

● Teriparatide increases BMD at the spine and hip, reducing the risk of vertebral and non-vertebral fractures in women and men with severe osteoporosis. Research has shown that in post menopausal women who have had vertebral fractures, teriparatide reduces the risk of further vertebral fractures by 65% and other fractures by 53%. In osteoporotic men, teriparatide increases BMD in the spine by an average 5% and in the hip by 1% compared to placebo.

Form

● A self-administered subcutaneous daily injection using a prefilled multi-dose delivery device (pen).

PBS listing

● Teriparatide is available in Australia for women and men with severe osteoporosis (BMD of -3.0 or lower) who have had 2 or more fractures due to minimal trauma. The patient needs to have experienced at least one symptomatic new fracture after at least 12 months continuous therapy with an anti-resorptive agent, or be intolerant of current first line agents.

● PBS-subsidised treatment must be initiated by a specialist but can be continued by a GP.

Side effects

● Common side effects include nausea, arthralgia, headaches, dizziness and injection-site reactions.

Precaution

● Treatment with teriparatide is limited to a lifetime maximum duration of 18 months. Informed consent is required.
Medicines available on the PBS for prevention of fractures

Men and women aged 70 years and over with a BMD T-Score of less than or equal to -2.5 or -3.0 (depending on medication prescribed) can receive treatment for osteoporosis on the PBS, without having sustained a fracture ie: for primary prevention.

The treatments listed by the PBS for this group include alendronate, risedronate and zoledronic acid. Denosumab is also available on the PBS for primary prevention in people aged 70 and older.

The PBS also subsidises some treatment for osteoporosis in patients of any age, who have had a minimal trauma fracture. Available treatments include alendronate, risedronate, zoledronic acid, denosumab and strontium ranolate.

Raloxifene is subsidised for the treatment of osteoporosis only in post menopausal women who have had a minimal trauma fracture.

Medication chart

<table>
<thead>
<tr>
<th>Name/s</th>
<th>Dosage</th>
<th>PBS Listing</th>
<th>Listing for Men</th>
<th>Contraindicated use: Bone preservation*</th>
<th>Most common side effects</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First line therapies</strong></td>
<td></td>
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<tr>
<td><strong>Oral/WI bisphosphonates</strong></td>
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<tr>
<td>Active ingredient: Alendronate (Various generics)</td>
<td>Various tablets available including daily and weekly Calcium may be included for the other 6 days</td>
<td>Established osteoporosis with minimal trauma OR aged 70 years or over with T-Score -2.5 or less</td>
<td>YES</td>
<td>YES</td>
<td>Can include pain in swallowing, upper gastrointestinal effects &amp; indigestion</td>
<td>Take on empty stomach first thing in morning, with recommended amount of water, stay upright for 30 minutes</td>
</tr>
<tr>
<td>Active ingredient: Risedronate (ACTONEL and generics)</td>
<td>Various tablets available: daily, weekly or monthly Calcium tablets or calcium +vitamin D capsules may also be included in the pack</td>
<td>Established osteoporosis with minimal trauma OR aged 70 years or over with T-Score -2.5 or less</td>
<td>YES</td>
<td>YES</td>
<td>As above</td>
<td>Take on empty stomach first thing in morning, with recommended amount of water, stay upright and do not eat anything for 30 minutes</td>
</tr>
<tr>
<td>Active ingredient: Zoledronic acid (ACLASTA)</td>
<td>1 infusion every 12 months</td>
<td>Established osteoporosis with a minimal trauma fracture OR aged 70 years or over with T-Score -3.0 or less</td>
<td>YES</td>
<td>YES</td>
<td>Fever, myalgia, flu-like illness and headache usually within 3 days of infusion</td>
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<tr>
<td><strong>SC RANK Ligand inhibitor/monoclonal antibody</strong></td>
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<tr>
<td>Active ingredient: Denosumab (PROLIA)</td>
<td>1 subcutaneous injection every 6 months</td>
<td>Established osteoporosis and a minimal trauma fracture OR aged over 70 or over years with T-Score -2.5 or less</td>
<td>YES</td>
<td>NO</td>
<td>Skin irritations, bone, joint or extremity pain, achings muscles, high cholesterol, stomach pain</td>
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<tr>
<td><strong>Oral strontium ranolate</strong></td>
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<tr>
<td>Active ingredient: Strontium ranelate (PROTOS)</td>
<td>1 sachet per day dissolved in water preferably at bedtime</td>
<td>People with established osteoporosis and a minimal trauma fracture.</td>
<td>YES</td>
<td>NO</td>
<td>Can include nausea, vomiting, diarrhoea, stomach pain or discomfort, headache or irritation in the mouth</td>
<td>Increased risk of cardiovascular events with this drug. Restricted to patients unable to use other medications. Do not use in patients with past or current heart disease or thyroidobembolism. Use with caution in patients with risk factors for these conditions.</td>
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<tr>
<td><strong>Oral serms</strong></td>
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<tr>
<td>Active ingredient: Raloxifene (EVISTA)</td>
<td>Daily tablet</td>
<td>Post menopausal women</td>
<td>NO</td>
<td>NO</td>
<td>Can worsen menopausal symptoms, increased risk of blood clots</td>
<td>Effective for spine but not hip</td>
</tr>
<tr>
<td><strong>Second line therapies</strong></td>
<td></td>
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<tr>
<td><strong>SC parathyroid hormone</strong></td>
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<tr>
<td>Active ingredient: Teriparatide (Forteo)</td>
<td>1 subcutaneous injection every 18 months</td>
<td>T-Score -3.0 or less AND 2 or more fractures due to minimal trauma with at least one new fracture after 12 mon 1/2s of bisphosphonate therapy</td>
<td>YES</td>
<td>NO</td>
<td>Nausea, arthralgia, headaches, dizziness and injection site reactions</td>
<td>Lifelong usage restricted to 18 months</td>
</tr>
</tbody>
</table>

*1 months at 7.5mg/day prednisolone or equivalent T-Score -1.5

Which first-line treatment should be prescribed?

Currently, no single antiresorptive therapy is appropriate for all patients with osteoporosis nor is clearly superior to other agents. The choice of therapy for a specific patient, therefore, should be made on an individual basis, taking into account the risk–benefit profiles of each therapy and the patient’s preferences.

- The choice of drug may be influenced by the mode of administration (e.g., annual, monthly, weekly or daily or by infusion for the bisphosphonates, or biannual subcutaneous injection for denosumab) or by the need for extra-skeletal benefits such as treatment of postmenopausal symptoms using HRT.
- If the aim is to reduce vertebral fractures, then any one of the first-line agents alendronate, denosumab, raloxifene, risedronate, or zoledronic acid, are suitable. Strontium ranelate may be used in patients without cardiovascular risk factors if other first line agents are unsuitable.
- If the aim is to reduce non-vertebral fractures, for example in women over 70-75 years with low femoral neck BMD, where the risk of hip-fracture is high, then a potent bisphosphonate, denosumab or strontium ranelate should be used. The SERM raloxifene has been demonstrated to prevent spinal fractures but does not prevent non-spinal fractures.

Bisphosphonates increase bone density at the spine and hip and reduce vertebral fracture risk in patients treated with glucocorticoids. There are no efficacy data on hip and non-vertebral fractures for these patients.

In men with osteoporosis there is evidence for the efficacy of bisphosphonates, teriparatide, strontium ranelate and denosumab in increasing bone density. The efficacy of combination therapies has been investigated but data are scarce and study sizes too small to determine whether fracture risk would be significantly reduced compared to monotherapy, although combined therapy may produce greater increases in BMD.

Evidence according to sex and fracture type

There is evidence for variable efficacy of osteoporosis medications based on sex and (in women) potential fracture site:

<table>
<thead>
<tr>
<th>Evidence in men and women</th>
<th>Evidence in men</th>
<th>Evidence in women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisphosphonates – Alendronate – Risedronate – Zoledronic acid</td>
<td>Yes</td>
<td>Yes (vertebral, non-vertebral, hip)</td>
</tr>
<tr>
<td>Denosumab</td>
<td>Yes</td>
<td>Yes (vertebral, non-vertebral, hip)</td>
</tr>
<tr>
<td>Strontium ranelate</td>
<td>Yes</td>
<td>Yes (vertebral, non-vertebral, hip)</td>
</tr>
<tr>
<td>HRT</td>
<td>–</td>
<td>Yes (vertebral, non-vertebral, hip with precautions)</td>
</tr>
<tr>
<td>SERMs – Raloxifene</td>
<td>–</td>
<td>Yes (vertebral)</td>
</tr>
<tr>
<td>Teriparatide</td>
<td>Yes</td>
<td>Yes (vertebral, non-vertebral)</td>
</tr>
<tr>
<td>Androgen</td>
<td>Yes (when hypogonadism is present)</td>
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</tbody>
</table>

Duration of treatment

In principle, therapy for osteoporosis should be ongoing, as stopping treatment could result in increased bone loss, structural damage and increased fracture risk. Many patients with osteoporosis have been on treatment for 5 years, 10 years or longer. The decision to continue long-term therapy will be based on the response to therapy, as well as any precautions that must be considered, such as those for HRT. Those patients with either a recent fracture or continuing osteoporosis at the femoral neck would be considered at ‘high risk’ and benefit the most from continuing with therapy.

The overall aim of therapy is to reduce the risk of fracture and prevent bone loss and this must be the focus of managing patient bone health, rather than length of treatment.

Compliance with therapy

As with many medications there are compliance issues with osteoporosis treatment. Reasons for non-compliance include adverse effects, cost of treatment, strict dosing requirements (with oral therapy), patient inability to detect improvement and a lack of motivation.

Therapy now includes a range of dosing regimens including – oral weekly, oral monthly, IV (annual) and SC injection (6 monthly) which may assist in improving compliance and persistence with therapy. Physicians should provide patients with a detailed explanation of their treatment, explaining therapeutic benefit so good compliance and persistence can be achieved.