

## **VI.2 Elements for a public summary**

### **VI.2.1 Overview of disease epidemiology**

**Osteoporosis** is a disease of the bones. It happens when you lose too much bone; make too little bone or both. As a result, bones become weak and can break from a minor fall or, in serious cases, even from simple actions, like sneezing or bumping into furniture.

Osteoporosis means “porous bone.” If you look at healthy bone under a microscope, you will see that parts of it look like a honeycomb. If you have osteoporosis, the holes and spaces in the honeycomb are much bigger than they are in healthy bone. This means your bones have lost density or mass and that the structure of your bone tissue has become abnormal. As your bones become less dense, they also become weaker and more likely to break.

Although women are at greater risk, men get osteoporosis too. If you think you can't get osteoporosis because you're a man, think again. As our population ages, even more men will get the disease.

Osteoporosis is often called the “silent disease,” because you could have it now or be at-risk without even realizing it. You can't feel your bones becoming weaker.

Currently it is estimated that over 200 million people worldwide suffer from this disease. Approximately 30% of all postmenopausal women have osteoporosis in the United States and in Europe. At least 40% of these women and 15-30% of men will sustain one or more fragility fractures in their remaining lifetime. Ageing of populations worldwide will be responsible for a major increase of the incidence of osteoporosis in postmenopausal women.

**Paget disease** is a localized disorder of bone remodeling that typically begins with excessive bone resorption followed by an increase in bone formation.

Paget's disease occurs in 1–2% of white adults over 50 and is more common in men. Prevalence increases substantially with age and by the eighth decade of life it may be present in approximately 8% of men and 5% of women. Paget disease is believed to develop in persons in the fifth decade of life and is most commonly diagnosed in the sixth decade. The incidence of Paget disease in persons older than 80 years is approximately 10%. There is a juvenile form of Paget disease, but it is very different from the adult form.

There is marked ethnic and geographical clustering, with the disease being common in some parts of the world but relatively rare in others. Clinical observations indicate that it is found more often in Europe, the US, Australia and New Zealand but is rare in Scandinavia, the Indian subcontinent, China, Japan and other countries in South East Asia.

A large European radiographic study showed that rates in the UK were higher than in most other western European countries. A further survey showed a marked focus of

Paget's disease in a cluster of six Lancashire. Over the past 25 years the prevalence and severity of disease has reduced substantially in the UK and New Zealand and remained fairly stable in the US.

### **VI.2.2 Summary of treatment benefits**

Risedronate belongs to a group of non-hormonal medicines called bisphosphonates which are used to treat bone diseases. It works directly on your bones to make them stronger and therefore less likely to break.

Bone is a living tissue. Old bone is constantly removed from your skeleton and replaced with new bone.

Postmenopausal osteoporosis is a condition occurring in women after the menopause where the bones become weaker, more fragile and more likely to break after a fall or strain.

Osteoporosis can also occur in men due to a number of causes including ageing and/or a low level of the male hormone, testosterone.

The spine, hip and wrist are the most likely bones to break, although this can happen to any bone in your body. Osteoporosis –related fractures can also cause back pain, height loss and a curved back. Many patients with osteoporosis have no symptoms and you may not even have known that you had it.

Risedronate is used to treat osteoporosis in women after menopause and in this way reduces the risk of fractures.

Risedronate is used for treatment of osteoporosis in men with high risk of fractures.

Risedronate is used for treatment of Paget's disease of the bone.

### **VI.2.3 Unknowns relating to treatment benefits**

In a number of published studies risedronate has shown benefits for non-approved indications. Risedronate is currently being evaluated in oral form for the treatment of hypercalcemia. Bisphosphonates also appear to be promising in the prevention of hypercalcemia in patients with breast carcinomas. Risedronate has also shown a beneficial effect in bone cancer or bone metastases. Risedronate decreased bone cancer-related bone destruction and pain-related behavior and decreased the spinal expression of glial fibrillary acidic protein. Risedronate is also given off-label in order to decrease bone resorption and increase bone density in women with anorexia nervosa and osteopenia.

While diuretics are the first-line therapy for hypercalciuria, bisphosphonates such as risedronate, are second-line therapy, according to physicians at the Lorain Kidney Stone Research Center of the Medical College of Ohio. The two classes of drugs may

be used separately or together, and their effectiveness has been documented by research.

Other off-label indications included patients with osteogenesis imperfecta, hyperparathyroidism. Other conditions reported as indication in small numbers were celiac disease, ankylosing spondylitis, cancer, hypogonadism, Addison's disease, osteochondrosis, osteodystrophy, nephrotic syndrome and chronic renal failure, some of which may reflect the prescribing context rather than the specific indication for risedronate.

#### VI.2.4 Summary of safety concerns

Risk in lay language ( <i>medical term</i> )	What is known	Preventability
<b>Important identified risks</b>		
If your doctor has told you that you have a condition called hypocalcaemia (a low blood calcium level) ( <i>Hypocalcaemia</i> )	<p>If you have low blood calcium before you start taking risedronate, it may get worse during treatment. Most people with low blood calcium levels do not have symptoms, but some people may have symptoms. Call your doctor right away if you have symptoms of low blood calcium such as:</p> <ul style="list-style-type: none"> <li>• Spasms, twitches, or cramps in your muscles</li> <li>• Numbness or tingling in your fingers, toes, or around your mouth</li> </ul> <p>Your doctor may prescribe calcium and vitamin D to help prevent low calcium levels in your blood, while you take Risedronate. Take calcium and vitamin D as your doctor tells you to.</p>	<p>Yes, your doctor should treat first your hypocalcaemia before starting risedronate therapy. Your doctor may prescribe calcium and vitamin D to help prevent low calcium levels in your blood, while you take Risedronate. Take calcium and vitamin D as your doctor tells you to.</p>
Inflammation of the coloured part of the eye ( <i>Iritis</i> ) Light sensitivity and/or red painful eyes with possible change in vision ( <i>Uveitis</i> )	<p>Iritis is an uncommon adverse reaction seen in clinical trials and during post-marketing experience.</p> <p>Uveitis is an uncommon adverse reaction seen in clinical trials and during post-marketing experience.</p>	<p>Inform your doctor if you experience inflammation of the eyes. The doctor based on individual benefit / risk assessment will decide if you continue treatment or not. You might be prescribed topical eye steroids in order to treat your reaction.</p>
If you are allergic (hypersensitive) to risedronate sodium or any of the other ingredients of Risedronate ( <i>Hypersensitivity and</i>	<p>Hypersensitivity and skin reactions, including angioedema, generalised rash, and bullous skin reactions, some severe have been reported during the post-marketing experience.</p>	<p>Call your doctor if you experience such type of reactions. Discontinuation of the treatment in some cases might be inevitable.</p>

<i>(skin reactions)</i>		
Severe jaw bone problems <i>(Osteonecrosis of the jaw)</i>	Osteonecrosis of the jaw generally associated with tooth extraction and/or local infection (including osteomyelitis) has been reported in patients with cancer receiving treatment regimens including primarily intravenously administered bisphosphonates. Many of these patients were also receiving chemotherapy and corticosteroids. Osteonecrosis of the jaw has also been reported in patients with osteoporosis receiving oral bisphosphonates.	Your doctor should examine your mouth before you start Risedronate. Your doctor may tell you to see your dentist before you start Risedronate. It is important for you to practice good mouth care during treatment with Risedronate. If you are under dental treatment or have to undergo dental surgery, tell your dentist that you are taking Risedronate.
<b>Important potential risks</b>		
If you had problems in the past with your oesophagus (the tube that takes food from your mouth to your stomach). For instance you may have had pain or difficulty in swallowing food (oesophagus irritation). If you have noticed inflammation and pain in the stomach (gastritis) <i>(Serious upper GI irritations)</i>	<p>Take Risedronate exactly as your doctor tells you. Your doctor may change your dose of Risedronate if needed.</p> <ul style="list-style-type: none"> <li>• <b>Risedronate works only if taken on an empty stomach.</b> <ul style="list-style-type: none"> <li>• Take 1 Risedronate tablet, <b>after</b> you get up for the day and <b>before</b> taking your first food, drink, or other medicine.</li> <li>• Take Risedronate while you are sitting or standing.</li> <li>• <b>Do not chew or suck on a tablet of Risedronate.</b> <ul style="list-style-type: none"> <li>• Swallow Risedronate tablet with a full glass of <u>plain water</u> only.</li> <li>• <b>Do not</b> take Risedronate with mineral water, coffee, tea, soda, or juice.</li> </ul> <p>After swallowing Risedronate tablet, wait at least 30 minutes:</p> <li>• Before you lie down. You may sit, stand or walk, and do normal activities like reading.</li> <li>• Before you take your first food or drink except for plain water.</li> <li>• Before you take other medicines, including antacids, calcium, and other supplements and vitamins.</li> </li></ul> <p><b>Do not lie down for at least 30 minutes after you take Risedronate and after you eat your first food of the day.</b></p> <p>Some people who take Risedronate may develop problems in the esophagus (the tube that connects the mouth and the</p> </li></ul>	<p>It is important that you take Risedronate exactly as prescribed to help lower your chance of getting esophagus problems. Stop taking Risedronate and call your doctor right away if you get chest pain, new or worsening heartburn, or have trouble or pain when you swallow.</p> <p>If you experience inflammation and pain in the stomach call your doctor immediately. The doctor based on individual benefit /risk assessment will decide if you continue treatment or not.</p>

	stomach). These problems include irritation, inflammation, or ulcers of the esophagus which may sometimes bleed. Gastritis is an uncommon adverse reaction seen in clinical trials.	
If you experience severe pain in your muscles <i>(Severe musculoskeletal pain)</i>	In post-marketing experience, risedronate may cause pain in bones, joints or muscles, rarely severe. Pain may start as soon as one day or up to several months after starting risedronate.	Call your doctor right away if you notice any of these side effects. Most patients had relief of symptoms after stopping the medication. A subset of patients had recurrence of symptoms when re-challenged with the same drug or another bisphosphonate. Consider discontinuing use if severe symptoms develop.
If you experience a medical condition called hepatitis. Hepatitis means inflammation of your liver. <i>(Serious hepatitis disorders)</i>	Hepatitis is a medical condition defined by the inflammation of the liver and characterized by the presence of inflammatory cells in the tissue of the organ. Hepatitis may occur with limited or no symptoms, but often leads to jaundice (icterus, yellowing of the skin and eyes), anorexia (poor appetite) and malaise.	Call your doctor right away if you notice any of these side effects. Your doctor should evaluate your condition and should consider discontinuing use if severe symptoms develop.
Unusual thigh bone fractures <i>(Atypical femoral fractures)</i>	Some people have developed unusual fractures in their thigh bone particularly on long-term treatment for osteoporosis. Symptoms of a fracture may include new or unusual pain in your hip, groin, or thigh.	Contact your doctor if you experience pain, weakness or discomfort in your thigh, hip or groin as this may be an early indication of a possible fracture of the thigh bone.

#### Important missing information

Risk	What is known
A common heart disorder called atrial fibrillation <i>(Atrial fibrillation)</i>	Information on the lack of data regarding the use of risedronate and the risk of atrial fibrillation is not included in the current SmPC. Concerning cardiac safety; bisphosphonates have been associated with increased incidence of atrial fibrillation. Despite that, in November 2008 the FDA stated that there is no clear association between oral bisphosphonate exposure and the incidence of atrial fibrillation.
Insufficient data on safety and efficacy in children and adolescents	Risedronate is not recommended for use in children and adolescents due to insufficient data on safety and efficacy. Osteoporosis usually is a disease that affects people aged 50 and above.
Insufficient evidence to support efficacy in the	The evidence to support efficacy of bisphosphonates including risedronate in the very elderly (>80 years) is limited. Data suggest that

very elderly (>80 years)	a more limited protection than this may be observed in the very elderly. This may be due to the increasing importance of non-skeletal factors for hip fracture with increasing age. In these trials, data analysed as a secondary endpoint indicated a decrease in the risk of new vertebral fractures in patients with low femoral neck BMD without vertebral fracture and in patients with low femoral neck BMD with or without vertebral fracture.
No formal interaction studies	No formal interaction studies have been performed, however no clinically relevant interactions with other medicinal products were found during clinical trials. <b>Tell your doctor about all the medicines you take</b> , including prescription and non-prescription medicines, vitamins and herbal supplements. Certain medicines may affect how Risedronate works. Especially tell your doctor if you take: <ul style="list-style-type: none"> <li>• antacids</li> <li>• aspirin</li> <li>• Non-steroidal Anti-Inflammatory (NSAID) medicines</li> </ul>
No adequate data in pregnant and breast-feeding women	There are no adequate data from the use of risedronate sodium in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown. Studies in animals have shown that a small amount of risedronate sodium is excreted into breast milk. It is unknown if risedronate sodium passes into human milk. Risedronate must not be used during pregnancy or by breast-feeding women.