RISEDRONATE SODIUM 5 MG, 30 MG AND 35 MG FILM-COATED TABLETS

PL 06464/2737-9

UKPAR

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LAY SUMMARY

On 10th November 2010, the MHRA granted Waymade PLC Marketing Authorisations (licences) for Risedronate Sodium 5 mg, 30 mg and 35 mg film-coated tablets.

Risedronate Sodium 5 mg, 30 mg and 35 mg film-coated tablets contain the active ingredient, risedronate sodium. Risedronate sodium belongs to a group of non-hormonal medicines called bisphosphonates which are used to treat bone diseases. Risedronate sodium works directly on your bones to make them stronger and therefore less likely to break.

Risedronate sodium 5 mg is used to:
- reduce the risk of vertebral fractures in women with postmenopausal osteoporosis. It also reduces the risk of hip fractures in women with established postmenopausal osteoporosis.
- prevent osteoporosis in postmenopausal women with an increased risk of osteoporosis.
- maintain or increase bone mass in postmenopausal women who have been on high doses of steroids drugs for a long time.

Risedronate sodium 30 mg is used to treat Paget’s disease of the bone.

Risedronate sodium 35 mg is used for the treatment of osteoporosis in:
- postmenopausal women, even if osteoporosis is severe. It reduces the risk of spinal and hip fractures.
- men.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Risedronate Sodium 5 mg, 30 mg and 35 mg film-coated tablets outweigh the risks; hence Marketing Authorisations have been granted.
RISEDRONATE SODIUM 5 MG, 30 MG AND 35 MG FILM-COATED TABLETS

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SCIENTIFIC DISCUSSION

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The UK granted Waymade PLC Marketing Authorisations for the medicinal products Risedronate Sodium 5 mg, 30 mg and 35 mg film-coated tablets (PL 06464/2737-9) on 10th November 2010. Risedronate Sodium 5 mg, 30 mg and 35 mg film-coated tablets are prescription only medicines (POM).

Risedronate Sodium 5 mg film-coated tablets are indicated for the:
- Treatment of postmenopausal osteoporosis, to reduce the risk of vertebral fractures.
- Treatment of established postmenopausal osteoporosis, to reduce the risk of hip fractures.
- Prevention of osteoporosis in postmenopausal women with increased risk of osteoporosis.
- Maintenance or increase of bone mass in postmenopausal women undergoing long-term (more than 3 months), systemic corticosteroid treatment at doses \( \geq 7.5 \text{mg/day prednisone or equivalent} \).

Risedronate Sodium 30 mg film-coated tablets are indicated for the treatment of Paget’s disease of the bone.

Risedronate Sodium 35 mg film-coated tablets are indicated for the treatment of:
- Treatment of postmenopausal osteoporosis, to reduce the risk of vertebral fractures.
- Treatment of established postmenopausal osteoporosis, to reduce the risk of hip fractures.
- Treatment of osteoporosis in men at high risk of fractures.

These applications for Risedronate Sodium 5 mg, 30 mg and 35 mg film-coated tablets are submitted under Article 10.1 of Directive 2001/83/EC, claiming to be generic medicinal products to Optinate 5 mg, 30 mg and 35 mg film-coated tablets, first authorised in the EA to Sanofi-Aventis AB in 7th October 1999.

The UK reference products are Actonel 5 mg, 30 mg (PL 00364/0070-1) and Actonel Once a Week 35 mg film-coated tablets (PL 00364/0080), first authorised to Proctor & Gamble Pharmaceuticals UK Limited in March 2000 and January 2003 (for PL 00364/0080).

Risedronate sodium is a pyridinyl bisphosphonate that inhibits osteoclast-mediated bone resorption and modulates bone metabolism.

Risedronate is pyrophosphate structurally and pharmacologically related to etidronate, pamidronate and alendronate. Like these other agents, risedronate is used for the prevention and treatment of osteoporosis and for the treatment of Paget's disease of bone. The drug can also be used in the treatment of bone metastasis. Bone is continually being formed and dissolved. By slowing down the rate at which bone is dissolved, risedronate increases the amount of bone.
In comparison with the other bisphosphonates, the likelihood of developing gastro-intestinal side effects is much lower with risedronate. Risedronate is more potent in blocking the dissolution of bone than etidronate and alendronate.

The pharmacovigilance system as described by the applicant fulfils the requirements. It also provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring.

The Marketing Authorisation Holder has provided adequate justification for not submitting a Risk Management Plan (RMP).
PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE
Risedronate Sodium
INN: Risedronate sodium
Chemical name: [l-Hydroxy-2- (3-pyridinyl)ethylidene] bisphosphonic acid monosodium salt

(1-Hydroxy-1-phosphono-2-pyridin-3-yl-ethyl)phosphonic acid monosodium salt

Structure:

![Structure of Risedronate Sodium]

Physical form: White to off-white crystalline powder.

Molecular formula: C$_7$H$_{10}$N NaO$_7$P$_2$. 2.5 H$_2$O
Molecular weight: 350.13 (as hemipentahydrate)

Risedronate sodium complies with in-house specifications.

Synthesis of the drug substance from the designated starting materials has been adequately described, and appropriate in-process controls and intermediate specifications are applied.

Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

All potential known impurities have been identified and characterised. Appropriate proof of structure data has been supplied for the active pharmaceutical ingredients.

An appropriate specification is provided for the active substance, with suitable test methods and limits. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification. Suitable Certificates of Analysis have been provided for all reference standards used.

Satisfactory specifications and Certificates of Analysis have been provided for all aspects of the container-closure system. A declaration has been provided that the primary packaging complies with current regulations concerning contact with foodstuff.

Appropriate stability data have been generated showing the active substance to be a physically and chemically stable drug, and supporting an appropriate retest period.
DRUG PRODUCT
Other ingredients
Other ingredients in the tablet core consist of pharmaceutical excipients lactose monohydrate, microcrystalline cellulose, crospovidone and magnesium stearate.

Ingredients in the film-coating are hypromellose, titanium dioxide (E171), macrogol, hydroxypropyl cellulose and colloidal anhydrous silica. The 5mg tablets have the additional excipient yellow iron oxide (E172). The 35mg tablets have the additional excipients yellow iron oxide (E172) and red iron oxide (E172).

All the ingredients with the exception of yellow iron oxide and red iron oxide comply with their relevant European Pharmacopoeia monographs. Yellow iron oxide and red iron oxide comply with in-house specifications.

None of the excipients used contain material of human origin. The supplier has confirmed that the magnesium stearate contained in this product is sourced from vegetable origin.

The applicant has provided a declaration that milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as those intended for human consumption.

Product development
The objective of the development programme was to produce products that could be considered generic medicinal products of Actonel 5 mg, 30 mg and Actonel Once a Week 35 mg film-coated tablets (Proctor & Gamble Pharmaceuticals UK Limited).

The reference product used in the bioequivalence study is Actonel 30 mg film-coated tablets, authorised in the Netherlands to Proctor & Gamble Pharmaceuticals Nedeland B.V. The Netherlands product is considered qualitatively and quantitatively similar to the reference product.

The applicant has provided a suitable product development section. Justifications for the use and amounts of each excipient have been provided and are valid. Comparative in vitro dissolution profiles have been provided for the proposed and originator products.

Manufacture
A description and flow-chart of the manufacturing method has been provided. Satisfactory batch formulae have been provided for the manufacture of the products. The manufacturing process has been validated and has shown satisfactory results. In-process controls are satisfactory based on batch data and controls on the finished product. Process validation data on pilot batches of each strength have been provided. The applicant has committed to perform process validation on commercial-scale batches of each strength.

Finished product specification
The finished product specifications are satisfactory. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specifications. Certificates of Analysis for all working standards used have been provided and are satisfactory.
**Container-Closure System**
The products are packaged in blisters composed of oriented polyamide, aluminium polyvinyl chloride (PVC) and aluminium foil. These blisters are then packaged into cardboard cartons.

Pack sizes are:
PL 06464/2737: 14, 20 (2 x 10), 28 (2 x 14), 30 (3 x 10), 84 (6 x 14) or 98 (7 x 14) tablets.
PL 06464/2738: 28 (2 x 14) or 30 (3 x 10) tablets.
PL 06464/2739: 4 or 12 (3 x 4) tablets.

Specifications and Certificates of Analysis have been provided. All primary product packaging complies with EU legislation regarding contact with food.

**Stability**
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf life of 2 years has been set, with special storage instructions ‘Do not store above 25°C’ and ‘Store in the original package.’ This is satisfactory.

**ADMINISTRATIVE**
**Expert Report**
A pharmaceutical expert report has been written by a suitably qualified person and is satisfactory.

**Summary of Product Characteristics (SmPC)**
These are pharmaceutically satisfactory.

**Labelling**
These are pharmaceutically satisfactory.

**Patient Information Leaflet (PIL)**
These are pharmaceutically satisfactory.

**MAA Form**
These are pharmaceutically satisfactory.

**Conclusion**
It is recommended that Marketing Authorisations are granted for these applications.
NON-CLINICAL ASSESSMENT

No new non-clinical data have been supplied with these applications and none are required for applications of this type.

The Marketing Authorisation Holder has provided adequate justification for not submitting an Environmental Risk Assessment.
CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY
To support the applications, the Marketing Authorisation Holder has included a single bioequivalence study:

A randomised, open label, two-treatment, two-sequence, four-period, crossover, single dose bioequivalence study comparing the pharmacokinetics of Risedronate Sodium 30 mg film-coated tablets (Test) versus Actonel® (Risedronate Sodium) 30 mg film-coated tablets (Reference) in healthy volunteers.

Blood sampling was performed pre-dose and up to 24 hours post dose in each treatment period. There was a washout period of 16 days. Pharmacokinetic parameters were measured from the plasma and statistically analysed.

Results from this study are presented below as log-transformed values:

Geometric Least Mean Squares and 90% Confidence Interval

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<th>Pharmacokinetic parameters of Risedronate sodium</th>
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<td>Treatment</td>
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<tr>
<td>Test</td>
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<tr>
<td>Reference</td>
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<td>Ratio (90% CI)</td>
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<td>0.94 – 1.15</td>
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The applicant adequately justified the use of the 30mg product for the bioequivalence study rather than the usual higher dose (35mg). Considering that the pharmacokinetics of risedronate sodium are linear over the therapeutic range, this is satisfactory.

The results for the primary variables indicated that the 90% confidence intervals test/reference ratio of geometric means for $\text{AUC}_{0-t}$ and $\text{C}_{\text{max}}$ for risedronate sodium lie within the normal 80-125% limits. Thus, bioequivalence has been shown between the test and reference products.

As the 30 mg strength product meets all the criteria as specified in the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 30 mg strength can be extrapolated to Risedronate Sodium 5 mg and 35 mg film-coated tablets.

Efficacy
No new data has been provided.

Safety
No new data has been provided.

Expert Reports
The clinical expert report has been written by a suitably qualified person and is satisfactory.

Patient Information Leaflet (PIL)
This is consistent with that for the reference product and is satisfactory.
LABELLING
These are satisfactory.

APPLICATION FORMS (MAA)
These are satisfactory.

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)
These are consistent with those for the reference products and are satisfactory.

DISCUSSION
The applicant has satisfactorily demonstrated bioequivalence between the test and reference products.

MEDICAL CONCLUSION
The bioequivalence study submitted has shown that Risedronate Sodium 5 mg, 30 mg and 35 mg film-coated tablets can be considered as generic medicinal products to the reference products Actonel 5 mg, 30 mg and Actonel Once a Week 35 mg film-coated tablets.

The grant of Marketing Authorisations is recommended for these applications.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Risedronate Sodium 5 mg, 30 mg and 35 mg film-coated tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL
No new preclinical data were submitted and none are required for applications of this type.

EFFICACY
Bioequivalence has been demonstrated between the applicant’s Risedronate Sodium 30 mg film-coated tablets and the reference product.

No new or unexpected safety concerns arise from these applications.

The SmPCs, PILs and labelling are satisfactory and consistent with those for the reference products.

RISK BENEFIT ASSESSMENT
The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant’s products and the reference products are interchangeable. Extensive clinical experience with risedronate sodium is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.
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STEPS TAKEN FOR ASSESSMENT

1 The MHRA received the Marketing Authorisation Applications on 13th October 2009.

2 Following standard checks and communication with the applicant the MHRA considered the applications valid on 26th October 2009.

3 Following assessment of the application, the MHRA requested further information relating to the clinical dossier on 9th September 2010.

Following assessment of the application, the MHRA requested further information relating to the quality dossier on, 25th March 2010 and 31st August 2010.

4 The applicant responded to the MHRA’s requests, providing further information on 24th September 2010 for the clinical section.

The applicant responded to the MHRA’s requests, providing further information on 31st July 2010 and 24th September 2010 for the quality section.

5 The applications were determined on 10th November 2010.
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STEPs TAKEN AFTER AUTHORISATION - SUMMARY
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Risedronate sodium 5 mg film-coated tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains 5 mg risedronate sodium (equivalent to 4.64 mg risedronic acid). For excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablets. Light-yellow coloured, round, film-coated tablets of 4.6 mm diameter, debossed with “J” on one side and “5” on the other.

4 CLINICAL PARTICULARS
4.1 THERAPEUTIC INDICATIONS
Treatment of postmenopausal osteoporosis, to reduce the risk of vertebral fractures. Treatment of established postmenopausal osteoporosis, to reduce the risk of hip fractures. Prevention of osteoporosis in postmenopausal women with increased risk of osteoporosis (see section 5.1).

To maintain or increase bone mass in postmenopausal women undergoing long-term (more than 3 months), systemic corticosteroid treatment at doses ≥ 7.5mg/day prednisone or equivalent.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION
The recommended daily dose in adults is one 5 mg tablet orally. The absorption of Risedronate sodium 5 mg is affected by food, thus to ensure adequate absorption patients should take Risedronate sodium 5 mg:
- Before breakfast: At least 30 minutes before the first food, other medicinal product or drink (other than plain water) of the day.

In the particular instance that before breakfast dosing is not practical, Risedronate sodium 5 mg can be taken between meals or in the evening at the same time everyday, with strict adherence to the following instructions, to ensure Risedronate sodium 5 mg is taken on an empty stomach:
- Between meals: Risedronate sodium 5 mg should be taken at least 2 hours before and at least 2 hours after any food, medicinal product or drink (other than plain water).
- In the evening: Risedronate sodium 5 mg should be taken at least 2 hours after the last food, medicinal product or drink (other than plain water) of the day. Risedronate sodium 5 mg should be taken at least 30 minutes before going to bed.

If an occasional dose is missed, Risedronate sodium 5 mg can be taken before breakfast, between meals, or in the evening according to the instructions above.

The tablets must be swallowed whole and not sucked or chewed. To aid delivery of the tablet to the stomach Risedronate sodium 5 mg is to be taken while in an upright position with a glass of plain water (>120 ml). Patients should not lie down for 30 minutes after taking the tablet (see section 4.4).

Supplemental calcium and vitamin D should be considered if the dietary intake is inadequate.

Elderly: No dosage adjustment is necessary since bioavailability, distribution and elimination were similar in elderly (>60 years of age) compared to younger subjects.

Renal Impairment: No dosage adjustment is required for those patients with mild to moderate renal impairment. The use of risedronate sodium is contraindicated in patients with severe renal impairment (creatinine clearance lower than 30 ml/min) (see sections 4.3 and 5.2).

Children: Safety and efficacy of Risedronate sodium 5 mg have not been established in children and adolescents.

4.3 CONTRAINDICATIONS
Hypersensitivity to risedronate sodium or to any of the excipients. Hypocalcaemia (see section 4.4).
Pregnancy and lactation.
Severe renal impairment (creatinine clearance <30ml/min).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE
Foods, drinks (other than plain water) and medicinal products containing polyvalent cations (such as calcium, magnesium, iron and aluminium) interfere with the absorption of bisphosphonates and should not be taken at the same time as Risedronate sodium 5 mg (see section 4.5) In order to achieve the intended efficacy, strict adherence to dosing recommendations is necessary (see section 4.2).

Efficacy of bisphosphonates in the treatment of postmenopausal osteoporosis is related to the presence of low bone mineral density (BMD T-score at hip or lumbar spine <-2.5 SD) and/or prevalent fracture.

High age or clinical risk factors for fracture alone are not reasons to initiate treatment of osteoporosis with a bisphosphonate.

The evidence to support efficacy of bisphosphonates including Risedronate sodium 5 mg in very elderly women (>80 years) is limited (see section 5.1).

Bisphosphonates have been associated with oesophagitis, gastritis oesophageal ulcerations and gastroduodenal ulcerations. Thus caution should be used:
• In patients who have a history of oesophageal disorders which delay oesophageal transit or emptying e.g. stricture or achalasia.
• In patients who are unable to stay in the upright position for at least 30 minutes after taking the tablet.
• If risedronate is given to patients with active or recent oesophageal or upper gastrointestinal problems.

Prescribers should emphasise to patients the importance of paying attention to the dosing instructions and be alert to any signs or symptoms of possible oesophageal reaction. The patients should be instructed to seek timely medical attention if they develop symptoms of oesophageal irritation such as dysphagia, pain on swallowing, retrosternal pain or new/worsened heartburn.

Hypocalcaemia should be treated before starting Risedronate sodium 5 mg therapy. Other disturbances of bone and mineral metabolism (e.g. parathyroid dysfunction, hypovitaminosis D) should be treated at the time of starting Risedronate sodium 5 mg therapy.

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.

A dental examination with appropriate preventive dentistry should be considered prior to treatment with bisphosphonates in patients with concomitant risk factors (e.g. cancer, chemotherapy, radiotherapy, corticosteroids, poor oral hygiene).

While on treatment, these patients should avoid invasive dental procedures if possible. For patients who develop osteonecrosis of the jaw while on bisphosphonate therapy, dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of osteonecrosis of the jaw.

Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

This medicine contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.
4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

No formal interaction studies have been performed, however no clinically relevant interactions with other medicinal products were found during clinical trials.

In the Risedronate sodium 5 mg Phase III osteoporosis studies, acetyl salicylic acid or NSAID use was reported by 33% and 45% of patients respectively.

If considered appropriate risedronate sodium may be used concomitantly with oestrogen supplementation.

Concomitant ingestion of medications containing polyvalent cations (e.g. calcium, magnesium, iron and aluminium) will interfere with the absorption of risedronate sodium (see section 4.4).

Risedronate sodium is not systemically metabolised, does not induce cytochrome P450 enzymes, and has low protein binding.

4.6 PREGNANCY AND LACTATION

There are no adequate data from the use of risedronate sodium in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Studies in animal indicate that a small amount of risedronate sodium pass into breast milk.

Risedronate sodium 5 mg must not be used during pregnancy or by breast-feeding women.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No effects on ability to drive and use machines have been observed.

4.8 UNDESIRABLE EFFECTS

Risedronate has been studied in phase III clinical trials involving more than 15,000 patients. The majority of undesirable effects observed in clinical trials were mild to moderate in severity and usually did not require cessation of therapy.

Adverse experiences reported in phase III clinical trials in postmenopausal women with osteoporosis treated for up to 36 months with risedronate 5mg/day (n=5020) or placebo (n=5048) and considered possibly or probably related to risedronate are listed below using the following convention (incidences versus placebo are shown in brackets): very common (≥1/10); common (≥1/100; <1/10); uncommon (≥1/1,000; <1/100); rare (≥1/10,000; <1/1,000); very rare (<1/10,000).

Nervous system disorders:
Common: headache (1.8% vs. 1.4%)

Eye disorders:
Uncommon: iritis*

Gastrointestinal disorders:
Common: constipation (5.0% vs. 4.8%), dyspepsia (4.5% vs. 4.1%), nausea (4.3% vs. 4.0%), abdominal pain (3.5% vs. 3.3%), diarrhoea (3.0% vs. 2.7%)
Uncommon: gastritis (0.9% vs. 0.7%), oesophagitis (0.9% vs. 0.9%), dysphagia (0.4% vs. 0.2%), duodenitis (0.2% vs. 0.1%), oesophageal ulcer (0.2% vs. 0.2%)
Rare: glossitis (<0.1% vs. 0.1%), oesophageal stricture (<0.1% vs. 0.0%)

Musculoskeletal and connective tissues disorders:
Common: musculoskeletal pain (2.1% vs. 1.9%)

Investigations (hepatobiliary):
Rare: abnormal liver function tests*

* No relevant incidences from Phase III osteoporosis studies; frequency based on adverse event/laboratory/rechallenge findings in earlier clinical trials.

Laboratory findings: Early, transient, asymptomatic and mild decreases in serum calcium and phosphate levels have been observed in some patients.
The following additional adverse reactions have been reported during post-marketing use (frequency unknown):

**Eye disorders:**
iritis, uveitis

**Musculoskeletal and connective tissues disorders:**
osteonecrosis of the jaw

**Skin and subcutaneous tissue disorders:**
- hypersensitivity and skin reactions, including angioedema, generalised rash, urticaria and bullous skin reactions, some severe including isolated reports of Stevens-Johnson syndrome and toxic epidermal necrolysis.
- hair loss.

**Immune system disorders:**
anaphylactic reaction

**Hepatobiliary disorders:**
serious hepatic disorders. In most of the reported cases the patients were also treated with other products known to cause hepatic disorders.

4.9 **OVERDOSE**

No specific information is available on the treatment of overdose with risedronate sodium.

Decreases in serum calcium following substantial overdose may be expected. Signs and symptoms of hypocalcaemia may also occur in some of these patients.

Milk or antacids containing magnesium, calcium or aluminium should be given to bind risedronate and reduce absorption of risedronate sodium. In cases of substantial overdose, gastric lavage may be considered to remove unabsorbed risedronate sodium.

5 **PHARMACOLOGICAL PROPERTIES**

5.1 **PHARMACODYNAMIC PROPERTIES**

Risedronate sodium is a pyridinyl bisphosphonate that binds to bone hydroxyapatite and inhibits osteoclast-mediated bone resorption. The bone turnover is reduced while the osteoblast activity and bone mineralisation is preserved. In preclinical studies risedronate sodium demonstrated potent anti-osteoclast and antiresorptive activity, and dose dependently increased bone mass and biomechanical skeletal strength. The activity of risedronate sodium was confirmed by measuring biochemical markers for bone turnover during pharmacodynamic and clinical studies. Decreases in biochemical markers of bone turnover were observed within 1 month and reached a maximum in 3-6 months.

**Treatment and Prevention of Postmenopausal Osteoporosis:**
A number of risk factors are associated with postmenopausal osteoporosis including low bone mass, low bone mineral density, early menopause, a history of smoking and a family history of osteoporosis. The clinical consequence of osteoporosis is fractures. The risk of fractures is increased with the number of risk factors.

The clinical programme studied the effect of risedronate sodium on the risk of hip and vertebral fractures and contained early and late postmenopausal women with and without fracture. Daily doses of 2.5 mg and 5 mg were studied and all groups, including the control groups, received calcium and vitamin D (if baseline levels were low). The absolute and relative risk of new vertebral and hip fractures were estimated by use of a time-to-first event analysis.

- Two placebo-controlled trials (n=3,661) enrolled postmenopausal women under 85 years with vertebral fractures at baseline. Risedronate sodium 5 mg daily given for 3 years reduced the risk of new vertebral fractures relative to the control group. In women with respectively at least 2 or at least 1 vertebral fractures, the relative risk reduction was 49% and 41%
respectively (incidence of new vertebral fractures with risedronate sodium 18.1% and 11.3%, with placebo 29.0% and 16.3%, respectively). The effect of treatment was seen as early as the end of the first year of treatment. Benefits were also demonstrated in women with multiple fractures at baseline. Risedronate sodium 5 mg daily also reduced the yearly height loss compared to the control group.

- Two further placebo controlled trials enrolled postmenopausal women above 70 years with or without vertebral fractures at baseline. Women 70-79 years were enrolled with femoral neck BMD T-score <−2.5 SD (manufacturer’s range, i.e. −2.5 SD using NHANES III) and at least one additional risk factor. Women >80 years could be enrolled on the basis of at least one non-skeletal risk factor for hip fracture or low bone mineral density at the femoral neck. Statistical significance of the efficacy of risedronate sodium versus placebo is only reached when the two treatment groups 2.5 mg and 5 mg are pooled. The following results are only based on a-posteriori analysis of subgroups defined by clinical practise and current definitions of osteoporosis:

  - In the subgroup of patients with femoral neck BMD T-score <−2.5SD (NHANES III) and at least one vertebral fracture at baseline, risedronate sodium given for 3 years reduced the risk of hip fractures by 46% relative to the control group (incidence of hip fractures in combined risedronate sodium 2.5 and 5 mg groups 3.8%, placebo 7.4%);

  - Data suggest that a more limited protection than this may be observed in the very elderly (>80 years). 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.

Risedronate sodium 5 mg daily given for 3 years increased bone mineral density (BMD) relative to control at the lumbar spine, femoral neck, trochanter and wrist and prevented bone loss at the mid-shaft radius.

- In a one-year follow-up off therapy after three years treatment with risedronate sodium 5 mg daily there was rapid reversibility of the suppressing effect of risedronate sodium on bone turnover rate.

- In postmenopausal women taking oestrogen, risedronate sodium 5 mg daily increased bone mineral density (BMD) at the femoral neck and mid-shaft radius only, compared to oestrogen alone.

- Bone biopsy samples from postmenopausal women treated with risedronate sodium 5 mg daily for 2 to 3 years, showed an expected moderate decrease in bone turnover. Bone formed during risedronate sodium treatment was of normal lamellar structure and bone mineralisation. These data together with the decreased incidence of osteoporosis related fractures at vertebral sites in women with osteoporosis appear to indicate no detrimental effect on bone quality.

- Endoscopic findings from a number of patients with a number of moderate to severe gastrointestinal complaints in both risedronate sodium and control patients indicated no evidence of treatment related gastric, duodenal or oesophageal ulcers in either group, although duodenitis was uncommonly observed in the risedronate sodium group.

- In a trial comparing before-breakfast dosing and dosing at other times of the day in women with postmenopausal osteoporosis, lumbar spine BMD gains were statistically higher with before-breakfast dosing.

In osteopenic postmenopausal women, risedronate sodium has shown superiority to placebo in increasing lumbar spine BMD at 12 and 24 months.

Corticosteroid Induced Osteoporosis: The clinical programme included patients initiating corticosteroid therapy (> 7.5 mg/day prednisone or equivalent) within the previous 3 months or
patients who had been taking corticosteroids for more than 6 months. Results of these studies demonstrate that:
- Risedronate sodium 5 mg daily given for one year maintains or increases bone mineral density (BMD) relative to control at the lumbar spine, femoral neck, and trochanter.
- Risedronate sodium 5 mg daily reduced the incidence of vertebral fractures, monitored for safety, relative to control at 1 year in pooled studies.
- Histological examination of bone biopsies from patients taking corticosteroids and risedronate sodium 5 mg daily did not show signs of disturbed mineralisation process.

5.2 PHARMACOKINETIC PROPERTIES

Absorption: Absorption after an oral dose is relatively rapid (tmax ~1 hour) and is independent of dose over the range studied (2.5 to 30 mg). Mean oral bioavailability of the tablet is 0.63% and is decreased when risedronate sodium is administered with food. Bioavailability was similar in men and women.

Distribution: The mean steady state volume of distribution is 6.3 l/kg in humans. Plasma protein binding is about 24%.

Metabolism: There is no evidence of systemic metabolism of risedronate sodium.

Elimination: Approximately half of the absorbed dose is excreted in urine within 24 hours, and 85% of an intravenous dose is recovered in the urine after 28 days. Mean renal clearance is 105 ml/min and mean total clearance is 122 ml/min, with the difference probably attributed to clearance due to adsorption to bone. The renal clearance is not concentration dependent, and there is a linear relationship between renal clearance and creatinine clearance. Unabsorbed risedronate sodium is eliminated unchanged in faeces. After oral administration the concentration-time profile shows three elimination phases with a terminal half-life of 480 hours.

Special populations:

Elderly: no dosage adjustment is necessary.

Acetyl salicylic acid/NSAID users: Among regular acetyl salicylic acid or NSAID users (3 or more days per week) the incidence of upper gastrointestinal adverse events in Risedronate sodium 5 mg treated patients was similar to that in control patients.

5.3 PRECLINICAL SAFETY DATA

In toxicological studies in rat and dog dose dependent liver toxic effects of risedronate sodium were seen, primarily as enzyme increases with histological changes in rat. The clinical relevance of these observations is unknown. Testicular toxicity occurred in rat and dog at exposures considered in excess of the human therapeutic exposure. Dose related incidences of upper airway irritation were frequently noted in rodents. Similar effects have been seen with other bisphosphonates. Lower respiratory tract effects were also seen in longer term studies in rodents, although the clinical significance of these findings is unclear. In reproduction toxicity studies at exposures close to clinical exposure ossification changes were seen in sternum and/or skull of foetuses from treated rats and hypocalcemia and mortality in pregnant females allowed to deliver. There was no evidence of teratogenesis at 3.2mg/kg/day in rat and 10mg/kg/day in rabbit, although data are only available on a small number of rabbits. Maternal toxicity prevented testing of higher doses. Studies on genotoxicity and carcinogenesis did not show any particular risks for humans.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Tablet core: Lactose monohydrate
- Microcrystalline cellulose
- Crospovidone
- Magnesium stearate.

Film coating: Hypermellose
- Titanium Dioxide
- Macrogol
- Hydroxypropyl Cellulose
Iron oxide yellow  
Colloidal Anhydrous Silica

6.2 INCOMPATIBILITIES  
Not applicable.

6.3 SHELF LIFE  
2 years.

6.4 SPECIAL PRECAUTIONS FOR STORAGE  
Do not store above 25°C. Store in the original package.

6.5 NATURE AND CONTENTS OF CONTAINER  
OPA-Al-PVC/aluminium foil blisters of 10 or 14 tablets in a cardboard carton.  
14, 20 (2 x 10), 28 (2 x 14), 30 (3 x 10), 84 (6 x 14) or 98 (7 x 14) tablets.  
Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL  
No special requirements.

7 MARKETING AUTHORISATION HOLDER  
Waymade Healthcare Plc trading as Sovereign Medical  
Sovereign House  
Miles Gray Road  
Basildon  
Essex, SS14 3FR  
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)  
PL 06464/2737

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION  
10/11/2010

10 DATE OF REVISION OF THE TEXT  
10/11/2010
1 NAME OF THE MEDICINAL PRODUCT
Risedronate sodium 30 mg film-coated tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains 30 mg risedronate sodium (equivalent to 27.8 mg risedronic acid).
For excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablets.
White to off-white, round, film-coated tablets of 9.1 mm diameter, debossed with “J” on one side and “30” on the other.

4 CLINICAL PARTICULARS
4.1 THERAPEUTIC INDICATIONS
Treatment of Paget’s disease of the bone.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION
The recommended daily dose in adults is one 30 mg tablet orally for 2 months. If re-treatment is considered necessary (at least two months post-treatment), a new treatment with the same dose and duration of therapy could be given. The absorption of Risedronate sodium 30 mg is affected by food, thus to ensure adequate absorption patients should take Risedronate sodium 30 mg:
* Before breakfast: At least 30 minutes before the first food, other medicinal product or drink (other than plain water) of the day.

In the particular instance that before breakfast dosing is not practical, Risedronate sodium 30 mg can be taken between meals or in the evening at the same time everyday, with strict adherence to the following instructions, to ensure Risedronate sodium 30 mg is taken on an empty stomach:
* Between meals: Risedronate sodium 30 mg should be taken at least 2 hours before and at least 2 hours after any food, medicinal product or drink (other than plain water).
* In the evening: Risedronate sodium 30 mg should be taken at least 2 hours after the last food, medicinal product or drink (other than plain water) of the day. Risedronate sodium 30 mg should be taken at least 30 minutes before going to bed.

If an occasional dose is missed, Risedronate sodium 30 mg can be taken before breakfast, between meals, or in the evening according to the instructions above.

The tablet must be swallowed whole and not sucked or chewed. To aid delivery of the tablet to the stomach Risedronate sodium 30 mg is to be taken while in an upright position with a glass of plain water (>120 ml). Patients should not lie down for 30 minutes after taking the tablet (see section 4.4).

Physicians should consider the administration of supplemental calcium and vitamin D if dietary intake is inadequate, especially as bone turnover is significantly elevated in Paget’s disease.

Elderly: No dosage adjustment is necessary since bioavailability, distribution and elimination were similar in elderly (>60 years of age) compared to younger subjects.

Renal Impairment: No dosage adjustment is required for those patients with mild to moderate renal impairment. The use of risedronate sodium is contraindicated in patients with severe renal impairment (creatinine clearance lower than 30 ml/min) (see sections 4.3 and 5.2).

Children: Safety and efficacy of Risedronate sodium 30 mg have not been established in children and adolescents.

4.3 CONTRAINDICATIONS
Hypersensitivity to risedronate sodium or to any of the excipients.
Hypocalcaemia (see section 4.4).
Pregnancy and lactation.
Severe renal impairment (creatinine clearance <30ml/min).
4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Foods, drinks (other than plain water) and medicinal products containing polyvalent cations (such as calcium, magnesium, iron and aluminium) interfere with the absorption of bisphosphonates and should not be taken at the same time as Risedronate sodium 30 mg (see section 4.5). In order to achieve the intended efficacy, strict adherence to dosing recommendations is necessary (see section 4.2).

Bisphosphonates have been associated with oesophagitis, gastritis oesophageal ulcerations and gastroduodenal ulcerations. Thus, caution should be used:

- In patients who have a history of oesophageal disorders which delay oesophageal transit or emptying e.g. stricture or achalasia.
- In patients who are unable to stay in the upright position for at least 30 minutes after taking the tablet.
- If risedronate is given to patients with active or recent oesophageal or upper gastrointestinal problems.

Prescribers should emphasise to patients the importance of paying attention to the dosing instructions and be alert to any signs or symptoms of possible oesophageal reaction. The patients should be instructed to seek timely medical attention if they develop symptoms of oesophageal irritation such as dysphagia, pain on swallowing, retrosternal pain or new/worsened heartburn.

Hypocalcaemia should be treated before starting Risedronate sodium 30 mg therapy. Other disturbances of bone and mineral metabolism (e.g. parathyroid dysfunction, hypovitaminosis D) should be treated at the time of starting Risedronate sodium 30 mg therapy.

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.

A dental examination with appropriate preventive dentistry should be considered prior to treatment with bisphosphonates in patients with concomitant risk factors (e.g. cancer, chemotherapy, radiotherapy, corticosteroids, poor oral hygiene).

While on treatment, these patients should avoid invasive dental procedures if possible. For patients who develop osteonecrosis of the jaw while on bisphosphonate therapy, dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of osteonecrosis of the jaw.

Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

This medicine contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

No formal interaction studies have been performed, however no clinically relevant interactions with other medicinal products were found during clinical trials.

Concomitant ingestion of medications containing polyvalent cations (e.g. calcium, magnesium, iron and aluminium) will interfere with the absorption of risedronate sodium (see section 4.4).

Risedronate sodium is not systemically metabolised, does not induce cytochrome P450 enzymes, and has low protein binding.
4.6 PREGNANCY AND LACTATION
There are no adequate data from the use of risedronate sodium in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3) The potential risk for humans is unknown. Studies in animal indicate that a small amount of risedronate sodium pass into breast milk.

Risedronate sodium 30 mg must not be used during pregnancy or by breast-feeding women.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
No effects on ability to drive and use machines have been observed.

4.8 UNDESIRABLE EFFECTS
Risedronate has been studied in phase III clinical trials involving more than 15,000 patients. The majority of undesirable effects observed in clinical trials were mild to moderate in severity and usually did not require cessation of therapy. Adverse experiences reported in phase III clinical trials in postmenopausal women with osteoporosis treated for up to 36 months with risedronate 5mg/day (n=5020) or placebo (n=5048) and considered possibly or probably related to risedronate are listed below using the following convention (incidences versus placebo are shown in brackets): very common (≥1/10); common (≥1/100; <1/10); uncommon (≥1/1,000; <1/100); rare (≥1/10,000; <1/1,000); very rare (<1/10,000).

Nervous system disorders:
Common: headache (1.8% vs. 1.4%)

Eye disorders:
Uncommon: iritis*

Gastrointestinal disorders:
Common: constipation (5.0% vs. 4.8%), dyspepsia (4.5% vs. 4.1%), nausea (4.3% vs. 4.0%), abdominal pain (3.5% vs. 3.3%), diarrhoea (3.0% vs. 2.7%)
Uncommon: gastritis (0.9% vs. 0.7%), oesophagitis (0.9% vs. 0.9%), dysphagia (0.4% vs. 0.2%), duodenitis (0.2% vs. 0.1%), oesophageal ulcer (0.2% vs. 0.2%)
Rare: glossitis (<0.1% vs. 0.1%), oesophageal stricture (<0.1% vs. 0.0%).

Musculoskeletal and connective tissues disorders:
Common: musculoskeletal pain (2.1% vs. 1.9%)

Investigations (hepatobiliary):
Rare: abnormal liver function tests*

* No relevant incidences from Phase III osteoporosis studies; frequency based on adverse event/laboratory/rechallenge findings in earlier clinical trials.

In a phase III Paget’s Disease clinical trial comparing risedronate vs. etidronate (61 patients in each group), the following additional adverse experiences considered possibly or probably drug related by investigators have been reported (incidence greater in risedronate than in etidronate): arthralgia (9.8% vs. 8.2%); amblyopia, apnoea, bronchitis, colitis, corneal lesion, cramps leg, dizziness, dry eye, flu syndrome, hypocalcaemia, myasthenia, neoplasm, nocturia, oedema peripheral, pain bone, pain chest, rash, sinusitis, tinnitus, and weight decrease (all at 1.6% vs. 0.0%).

Laboratory findings: Early, transient, asymptomatic and mild decreases in serum calcium and phosphate levels have been observed in some patients.

The following additional adverse reactions have been reported during post-marketing use (frequency unknown):

Eye disorders:
iritis, uveitis

Musculoskeletal and connective tissues disorders:
osteonecrosis of the jaw
**Skin and subcutaneous tissue disorders:**
Hypersensitivity and skin reactions, including angioedema, generalised rash, urticaria and bullous skin reactions, some severe including isolated reports of Stevens-Johnson syndrome and toxic epidermal necrolysis.

Hair loss.

**Immune system disorders:**
anaphylactic reaction

**Hepatobiliary disorders:**
Serious hepatic disorders. In most of the reported cases the patients were also treated with other products known to cause hepatic disorders.

### 4.9 OVERDOSE

No specific information is available on the treatment of overdose with risedronate sodium. Decreases in serum calcium following substantial overdose may be expected. Signs and symptoms of hypocalcaemia may also occur in some of these patients. Milk or antacids containing magnesium, calcium or aluminium should be given to bind risedronate and reduce absorption of risedronate sodium. In cases of substantial overdose, gastric lavage may be considered to remove unabsorbed risedronate sodium.

### 5 PHARMACOLOGICAL PROPERTIES

#### 5.1 PHARMACODYNAMIC PROPERTIES

**Pharmaco-therapeutic group:** Bisphosphonates  
**ATC Code:** M05 BA07

Risedronate sodium is a pyridinyl bisphosphonate that binds to bone hydroxyapatite and inhibits osteoclast-mediated bone resorption. The bone turnover is reduced while the osteoblast activity and bone mineralisation is preserved.

**Paget’s disease of the bone:** In the clinical programme Risedronate sodium 30 mg was studied in patients with Paget’s disease. After treatment with Risedronate sodium 30 mg/day for 2 months the following was seen:

- Serum alkaline phosphatase normalised in 77% of patients compared to 11% in the control group (etidronate 400 mg/day for 6 months). Significant reductions were observed in urinary hydroxyproline/creatinine and urinary deoxypyridinoline/creatinine

- Radiographs taken at baseline and after 6 months demonstrated a decrease in the extent of osteolytic lesions in both the appendicular and axial skeleton. No new fractures were observed.

The observed response was similar in pagetic patients regardless of whether they had previously received other treatments for Paget’s disease, or the severity of the disease.

53% of patients followed for 18 months after initiation of a single 2 month course of Risedronate sodium 30 mg remained in biochemical remission.

In a trial comparing before-breakfast dosing and dosing at other times of the day in women with postmenopausal osteoporosis, lumbar spine BMD gains were statistically higher with before-breakfast dosing.

#### 5.2 PHARMACOKINETIC PROPERTIES

**Absorption:** Absorption after an oral dose is relatively rapid (tmax ~1 hour) and is independent of dose over the range studied (2.5 to 30 mg). Mean oral bioavailability of the tablet is 0.63% and is decreased when risedronate sodium is administered with food. Bioavailability was similar in men and women.

**Distribution:** The mean steady state volume of distribution is 6.3 l/kg in humans. Plasma protein binding is about 24%.

**Metabolism:** There is no evidence of systemic metabolism of risedronate sodium.
Elimination: Approximately half of the absorbed dose is excreted in urine within 24 hours, and 85% of an intravenous dose is recovered in the urine after 28 days. Mean renal clearance is 105 ml/min and mean total clearance is 122 ml/min, with the difference probably attributed to clearance due to adsorption to bone. The renal clearance is not concentration dependent, and there is a linear relationship between renal clearance and creatinine clearance. Unabsorbed risedronate sodium is eliminated unchanged in faeces. After oral administration the concentration-time profile shows three elimination phases with a terminal half-life of 480 hours.

Special populations: Elderly: no dosage adjustment is necessary.

5.3 PRECLINICAL SAFETY DATA
In toxicological studies in rat and dog dose dependent liver toxic effects of risedronate sodium were seen, primarily as enzyme increases with histological changes in rat. The clinical relevance of these observations is unknown. Testicular toxicity occurred in rat and dog at exposures considered in excess of the human therapeutic exposure. Dose related incidences of upper airway irritation were frequently noted in rodents. Similar effects have been seen with other bisphosphonates. Lower respiratory tract effects were also seen in longer term studies in rodents, although the clinical significance of these findings is unclear. In reproduction toxicity studies at exposures close to clinical exposure ossification changes were seen in sternum and/or skull of foetuses from treated rats and hypocalcemia and mortality in pregnant females allowed to deliver. There was no evidence of teratogenesis at 3.2mg/kg/day in rat and 10mg/kg/day in rabbit, although data are only available on a small number of rabbits. Maternal toxicity prevented testing of higher doses. Studies on genotoxicity and carcinogenesis did not show any particular risks for humans.

6 PHARMACEUTICAL PARTICULARS
6.1 LIST OF EXCIPIENTS
Tablet core: Lactose monohydrate
Microcrystalline cellulose
Crocspovidone
Magnesium stearate.

Film coating: Hypromellose
Macrogol
Hydroxypropyl Cellulose
Colloidal Anhydrous Silica
Titanium dioxide E171.

6.2 INCOMPATIBILITIES
Not applicable.

6.3 SHELF LIFE
2 years.

6.4 SPECIAL PRECAUTIONS FOR STORAGE
Do not store above 25°C. Store in the original package.

6.5 NATURE AND CONTENTS OF CONTAINER
OPA-Al-PVC/aluminium foil blisters of 10 or 14 tablets in a cardboard carton.
28 (2 x 14) or 30 (3 x 10) tablets.
Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Waymade Healthcare Plc trading as Sovereign Medical
Sovereign House
Miles Gray Road
Basildon
Essex, SS14 3FR
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 06464/2738

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORIZATION
10/11/2010

10 DATE OF REVISION OF THE TEXT
10/11/2010
1 NAME OF THE MEDICINAL PRODUCT
Risedronate sodium 35 mg film-coated tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains 35 mg risedronate sodium (equivalent to 32.5 mg risedronic acid).
For excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet.
Light orange coloured, round, film-coated tablets of 9.1 mm diameter, debossed with “J” on one side and “35” on the other.

4 CLINICAL PARTICULARS
4.1 THERAPEUTIC INDICATIONS
Treatment of postmenopausal osteoporosis, to reduce the risk of vertebral fractures. Treatment of established postmenopausal osteoporosis, to reduce the risk of hip fractures (see section 5.1).
Treatment of osteoporosis in men at high risk of fractures (see section 5.1).

4.2 POSOLOGY AND METHOD OF ADMINISTRATION
The recommended dose in adults is one 35 mg tablet orally once a week. The tablet should be taken on the same day each week.
The absorption of risedronate sodium is affected by food, thus to ensure adequate absorption patients should take Risedronate sodium 35 mg:
• Before breakfast: At least 30 minutes before the first food, other medicinal product or drink (other than plain water) of the day.

Patients should be instructed that if a dose is missed, one Risedronate sodium 35 mg tablet should be taken on the day that the tablet is remembered. Patients should then return to taking one tablet once a week on the day the tablet is normally taken. Two tablets should not be taken on the same day.

The tablet must be swallowed whole and not sucked or chewed. To aid delivery of the tablet to the stomach Risedronate sodium 35 mg is to be taken while in an upright position with a glass of plain water (>120 ml). Patients should not lie down for 30 minutes after taking the tablet (see section 4.4).

Supplemental calcium and vitamin D should be considered if the dietary intake is inadequate.

Elderly: No dosage adjustment is necessary since bioavailability, distribution and elimination were similar in elderly (>60 years of age) compared to younger subjects.

This has also been shown in the very elderly, 75 years old and above postmenopausal population.

Renal Impairment: No dosage adjustment is required for those patients with mild to moderate renal impairment. The use of risedronate sodium is contraindicated in patients with severe renal impairment (creatinine clearance lower than 30ml/min) (see sections 4.3 and 5.2).

Children: Safety and efficacy of Risedronate sodium 35 mg have not been established in children and adolescents.

4.3 CONTRAINDICATIONS
Hypersensitivity to risedronate sodium or to any of the excipients.
Hypocalcaemia (see section 4.4).
Pregnancy and lactation.
Severe renal impairment (creatinine clearance <30ml/min).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE
Foods, drinks (other than plain water) and medicinal products containing polyvalent cations (such as calcium, magnesium, iron and aluminium) interfere with the absorption of bisphosphonates and should not be taken at the same time as Risedronate sodium 35 mg (see section 4.5). In order to achieve the intended efficacy, strict adherence to dosing recommendations is necessary (see section 4.2).
Efficacy of bisphosphonates in the treatment of osteoporosis is related to the presence of low bone mineral density and/or prevalent fracture.

High age or clinical risk factors for fracture alone are not sufficient reasons to initiate treatment of osteoporosis with a bisphosphonate.

The evidence to support efficacy of bisphosphonates including risedronate in the very elderly (>80 years) is limited (see section 5.1).

Bisphosphonates have been associated with oesophagitis, gastritis, oesophageal ulcerations and gastroduodenal ulcerations. Thus, caution should be used:

- In patients who have a history of oesophageal disorders which delay oesophageal transit or emptying e.g. stricture or achalasia
- In patients who are unable to stay in the upright position for at least 30 minutes after taking the tablet.
- If risedronate is given to patients with active or recent oesophageal or upper gastrointestinal problems.

Prescribers should emphasise to patients the importance of paying attention to the dosing instructions and be alert to any signs and symptoms of possible oesophageal reaction. The patients should be instructed to seek timely medical attention if they develop symptoms of oesophageal irritation such as dysphagia, pain on swallowing, retrosternal pain or new/worsened heartburn.

Hypocalcaemia should be treated before starting Risedronate sodium 35 mg therapy. Other disturbances of bone and mineral metabolism (i.e. parathyroid dysfunction, hypovitaminosis D) should be treated at the time of starting Risedronate sodium 35 mg therapy.

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.

A dental examination with appropriate preventive dentistry should be considered prior to treatment with bisphosphonates in patients with concomitant risk factors (e.g. cancer, chemotherapy, radiotherapy, corticosteroids, poor oral hygiene).

While on treatment, these patients should avoid invasive dental procedures if possible. For patients who develop osteonecrosis of the jaw while on bisphosphonate therapy, dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of osteonecrosis of the jaw.

Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

This medicine contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

No formal interaction studies have been performed, however no clinically relevant interactions with other medicinal products were found during clinical trials.

In the risedronate sodium Phase III osteoporosis studies with daily dosing, acetyl salicylic acid or NSAID use was reported by 33% and 45% of patients respectively. In the Phase III once a week study in postmenopausal women, acetyl salicylic acid or NSAID use was reported by 57% and 40% of patients respectively. Among regular acetyl salicylic acid or NSAID users (3 or more days per week) the incidence of upper gastrointestinal adverse events in risedronate sodium treated patients was similar to that in control patients.

If considered appropriate risedronate sodium may be used concomitantly with oestrogen supplementation (for women only).
Concomitant ingestion of medications containing polyvalent cations (e.g. calcium, magnesium, iron and aluminium) will interfere with the absorption of Risedronate sodium 35 mg (see section 4.4).

Risedronate sodium is not systemically metabolised, does not induce cytochrome P450 enzymes, and has low protein binding.

4.6 PREGNANCY AND LACTATION
There are no adequate data from the use of risedronate sodium in pregnant women. Studies in animals have shown reproductive toxicity (see 5.3). The potential risk for humans is unknown. Studies in animal indicate that a small amount of risedronate sodium pass into breast milk.

Risedronate sodium 35 mg must not be used during pregnancy or by breast-feeding women.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
No effects on ability to drive and use machines have been observed.

4.8 UNDESIRABLE EFFECTS
Risedronate sodium has been studied in phase III clinical trials involving more than 15,000 patients. The majority of undesirable effects observed in clinical trials were mild to moderate in severity and usually did not require cessation of therapy.

Adverse experiences reported in phase III clinical trials in postmenopausal women with osteoporosis treated for up to 36 months with risedronate sodium 5mg/day (n=5020) or placebo (n=5048) and considered possibly or probably related to risedronate sodium are listed below using the following convention (incidences versus placebo are shown in brackets): very common ($\geq$1/10); common ($\geq$1/100; <1/10); uncommon ($\geq$1/1,000; <1/100); rare ($\geq$1/10,000; <1/1,000); very rare (<1/10,000).

Nervous system disorders:
Common: headache (1.8% vs. 1.4%)

Eye disorders:
Uncommon: iritis*

Gastrointestinal disorders:
Common: constipation (5.0% vs. 4.8%), dyspepsia (4.5% vs. 4.1%), nausea (4.3% vs. 4.0%), abdominal pain (3.5% vs. 3.3%), diarrhoea (3.0% vs. 2.7%) Uncommon: gastritis (0.9% vs. 0.7%), oesophagitis (0.9% vs. 0.9%), dysphagia (0.4% vs. 0.2%), duodenitis (0.2% vs. 0.1%), oesophageal ulcer (0.2% vs. 0.2%) Rare: glossitis (<0.1% vs. 0.1%), oesophageal stricture (<0.1% vs. 0.0%),

Musculoskeletal and connective tissues disorders:
Common: musculoskeletal pain (2.1% vs. 1.9%)

Investigations:
Rare: abnormal liver function tests*

* No relevant incidences from Phase III osteoporosis studies; frequency based on adverse event/laboratory/rechallenge findings in earlier clinical trials.

In a one-year, double-blind, multicentre study comparing risedronate sodium 5 mg daily (n=480) and risedronate sodium 35 mg weekly (n=485) in postmenopausal women with osteoporosis, the overall safety and tolerability profiles were similar. The following additional adverse experiences considered possibly or probably drug related by investigators have been reported (incidence greater in risedronate 35 mg than in risedronate sodium 5 mg group): gastrointestinal disorder (1.6% vs. 1.0%) and pain (1.2% vs. 0.8%).

In a 2-year study in men with osteoporosis, the overall safety and tolerability were similar between the treatment and the placebo groups. Adverse experiences were consistent with those previously observed in women.
Laboratory findings: Early, transient, asymptomatic and mild decreases in serum calcium and phosphate levels have been observed in some patients.

The following additional adverse reactions have been reported during post-marketing use (frequency unknown):

Eye disorders:
iritis, uveitis

Musculoskeletal and connective tissues disorders:
osteonecrosis of the jaw

Skin and subcutaneous tissue disorders:
hypersensitivity and skin reactions, including angioedema, generalised rash, urticaria and bullous skin reactions, some severe including isolated reports of Stevens Johnson syndrome and toxic epidermal necrolysis.

Irritation

Hair loss

Immune system disorders:
anaphylactic reaction

Hepatobiliary disorders:
serious hepatic disorders. In most of the reported cases the patients were also treated with other products known to cause hepatic disorders.

4.9 OVERDOSE
No specific information is available on the treatment of overdose with risedronate sodium. Decreases in serum calcium following substantial overdose may be expected. Signs and symptoms of hypocalcaemia may also occur in some of these patients.

Milk or antacids containing magnesium, calcium or aluminium should be given to bind risedronate and reduce absorption of risedronate sodium. In cases of substantial overdose, gastric lavage may be considered to remove unabsorbed risedronate sodium.

5 PHARMACOLOGICAL PROPERTIES
5.1 PHARMACODYNAMIC PROPERTIES
Pharmaco-therapeutic group: Bisphosphonates
ATC Code: M05BA07.

Risedronate sodium is a pyridinyl bisphosphonate that binds to bone hydroxyapatite and inhibits osteoclast-mediated bone resorption. The bone turnover is reduced while the osteoblast activity and bone mineralisation is preserved. In preclinical studies risedronate sodium demonstrated potent anti-osteoclast and antiresorptive activity, and dose dependently increased bone mass and biomechanical skeletal strength. The activity of risedronate sodium was confirmed by measuring biochemical markers for bone turnover during pharmacodynamic and clinical studies. In studies of postmenopausal women, decreases in biochemical markers of bone turnover were observed within 1 month and reached a maximum in 3-6 months. Decreases in biochemical markers of bone turnover were similar with Risedronate sodium 35 mg and Risedronate sodium 5 mg daily at 12 months.

In a study in men with osteoporosis, decreases in biochemical markers of bone turnover were observed at the earliest time point of 3 months and continued to be observed at 24 months.

Treatment of Postmenopausal Osteoporosis:
A number of risk factors are associated with postmenopausal osteoporosis including low bone mass, low bone mineral density, early menopause, a history of smoking and a family history of osteoporosis. The clinical consequence of osteoporosis is fractures. The risk of fractures is increased with the number of risk factors.
Based on effects on mean change in lumbar spine BMD, risedronate sodium 35 mg (n=485) was shown to be equivalent to risedronate sodium 5 mg daily (n=480) in a one-year, double-blind, multicentre study of postmenopausal women with osteoporosis.

The clinical programme for risedronate sodium administered once daily studied the effect of risedronate sodium on the risk of hip and vertebral fractures and contained early and late postmenopausal women with and without fracture. Daily doses of 2.5 mg and 5 mg were studied in all groups, including the control groups, receiving calcium and vitamin D (if baseline levels were low). The absolute and relative risk of new vertebral and hip fractures were estimated by use of a time-to-first event analysis.

- Two placebo-controlled trials (n=3,661) enrolled postmenopausal women under 85 years with vertebral fractures at baseline. Risedronate sodium 5 mg daily given for 3 years reduced the risk of new vertebral fractures relative to the control group. In women with respectively at least 2 or at least 1 vertebral fractures, the relative risk reduction was 49% and 41% respectively (incidence of new vertebral fractures with risedronate sodium 18.1% and 11.3%, with placebo 29.0% and 16.3%, respectively). The effect of treatment was seen as early as the end of the first year of treatment. Benefits were also demonstrated in women with multiple fractures at baseline. Risedronate sodium 5 mg daily also reduced the yearly height loss compared to the control group.

- Two further placebo controlled trials enrolled postmenopausal women above 70 years with or without vertebral fractures at baseline. Women 70-79 years were enrolled with femoral neck BMD T-score <-3 SD (manufacturer’s range, i.e. -2.5 SD using NHANES III) and at least one additional risk factor. Women >80 years could be enrolled on the basis of at least one non-skeletal risk factor for hip fracture or low bone mineral density at the femoral neck. Statistical significance of the efficacy of risedronate versus placebo is only reached when the two treatment groups 2.5 mg and 5 mg are pooled. The following results are only based on *a-posteriori* analysis of subgroups defined by clinical practise and current definitions of osteoporosis:

  - In the subgroup of patients with femoral neck BMD T-score <-2.5SD (NHANES III) and at least one vertebral fracture at baseline, risedronate sodium given for 3 years reduced the risk of hip fractures by 46% relative to the control group (incidence of hip fractures in combined risedronate sodium 2.5 and 5 mg groups 3.8%, placebo 7.4%);

  - Data suggest that a more limited protection than this may be observed in the very elderly (>80 years). 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.

- Risedronate sodium 5 mg daily given for 3 years increased bone mineral density (BMD) relative to control at the lumbar spine, femoral neck, trochanter and wrist and maintained bone density at the mid-shaft radius.

  - In a one-year follow-up off therapy after three years treatment with risedronate sodium 5 mg daily there was rapid reversibility of the suppressing effect of risedronate sodium on bone turnover rate.

  - Bone biopsy samples from postmenopausal women treated with risedronate sodium 5 mg daily for 2 to 3 years, showed an expected moderate decrease in bone turnover. Bone formed during risedronate sodium treatment was of normal lamellar structure and bone mineralisation. These data together with the decreased incidence of osteoporosis related fractures at vertebral sites in women with osteoporosis appear to indicate no detrimental effect on bone quality.

Endoscopic findings from a number of patients with a number of moderate to severe gastrointestinal complaints in both risedronate sodium and control patients indicated no evidence of treatment related gastric, duodenal or oesophageal ulcers in either group, although duodenitis was uncommonly observed in the risedronate sodium group.

Treatment of Osteoporosis in Men
Risedronate sodium 35mg once a week demonstrated efficacy in men with osteoporosis (age range 36 to 84 years) in a 2-year, double-blind, placebo-controlled study in 284 patients (risedronate sodium 35mg n = 191). All patients received supplemental calcium and vitamin D.

Increases in BMD were observed as early as 6 months following initiation of risedronate sodium treatment. Risedronate sodium 35mg once a week produced mean increases in BMD at the lumbar spine, femoral neck, trochanter and total hip compared to placebo after 2 years of treatment. Antifracture efficacy was not demonstrated in this study.

The bone effect (BMD increase and BTM decrease) of risedronate sodium is similar in males and females.

5.2 PHARMACOKINETIC PROPERTIES

Absorption: Absorption after an oral dose is relatively rapid (tmax ~1 hour) and is independent of dose over the range studied (single dose study, 2.5 to 30 mg; multiple dose studies, 2.5 to 5 mg daily and up to 50 mg dosed weekly). Mean oral bioavailability of the tablet is 0.63% and is decreased when risedronate sodium is administered with food. Bioavailability was similar in men and women.

Distribution: The mean steady state volume of distribution is 6.3 l/kg in humans. Plasma protein binding is about 24%.

Metabolism: There is no evidence of systemic metabolism of risedronate sodium.

Elimination: Approximately half of the absorbed dose is excreted in urine within 24 hours, and 85% of an intravenous dose is recovered in the urine after 28 days. Mean renal clearance is 105 ml/min and mean total clearance is 122 ml/min, with the difference probably attributed to clearance due to adsorption to bone. The renal clearance is not concentration dependent, and there is a linear relationship between renal clearance and creatinine clearance.

Unabsorbed risedronate sodium is eliminated unchanged in faeces. After oral administration the concentration-time profile shows three elimination phases with a terminal half-life of 480 hours.

Special populations

Elderly: no dosage adjustment is necessary.

Acetyl salicylic acid/NSAID users: Among regular acetyl salicylic acid or NSAID users (3 or more days per week) the incidence of upper gastrointestinal adverse events in risedronate sodium treated patients was similar to that in control patients.

5.3 PRECLINICAL SAFETY DATA

In toxicological studies in rat and dog dose dependent liver toxic effects of risedronate sodium were seen, primarily as enzyme increases with histological changes in rat. The clinical relevance of these observations is unknown. Testicular toxicity occurred in rat and dog at exposures considered in excess of the human therapeutic exposure. Dose related incidences of upper airway irritation were frequently noted in rodents. Similar effects have been seen with other bisphosphonates. Lower respiratory tract effects were also seen in longer term studies in rodents, although the clinical significance of these findings is unclear. In reproduction toxicity studies at exposures close to clinical exposure ossification changes were seen in sternum and/or skull of foetuses from treated rats and hypocalcemia and mortality in pregnant females allowed to deliver. There was no evidence of teratogenesis at 3.2mg/kg/day in rat and 10mg/kg/day in rabbit, although data are only available on a small number of rabbits.

Maternal toxicity prevented testing of higher doses. Studies on genotoxicity and carcinogenesis did not show any particular risks for humans.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Tablet core: lactose monohydrate
microcrystalline cellulose
crospovidone
magnesium stearate
Film coating: Iron Oxide yellow E172
Iron Oxide red E172
Hypermellose
Macrogol
Hydroxypropyl Cellulose
Colloidal Anhydrous Silica
Titanium dioxide E171

6.2 INCOMPATIBILITIES
Not applicable.

6.3 SHELF LIFE
2 years.

6.4 SPECIAL PRECAUTIONS FOR STORAGE
Do not store above 25°C. Store in the original package.

6.5 NATURE AND CONTENTS OF CONTAINER
OPA-Al-PVC/aluminium foil blisters of 4 tablets in a cardboard carton.
4 or 12 (3 x 4) tablets.
Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
No special requirements.

7 MARKETING AUTHORITY HOLDER
Waymade Healthcare Plc trading as Sovereign Medical
Sovereign House
Miles Gray Road
Basildon
Essex, SS14 3FR
United Kingdom

8 MARKETING AUTHORITY NUMBER(S)
PL 06464/2739

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
10/11/2010

10 DATE OF REVISION OF THE TEXT
10/11/2010
PACKAGE LEAFLET: INFORMATION FOR THE USER

Risedronate sodium 5 mg film-coated tablets

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects becomes severe, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Risedronate sodium 5 mg is and what it is used for
2. Before you take Risedronate sodium 5 mg
3. How to take Risedronate sodium 5 mg
4. Possible side effects
5. How to store Risedronate sodium 5 mg
6. Further information

1. WHAT RISEDRONATE SODIUM 5 MG IS AND WHAT IT IS USED FOR

Risedronate sodium 5 mg 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.

Osteoporosis is a disease that causes bones to become more fragile. Osteoporosis is common in women after the menopause and is also more likely to occur in women who have reached the menopause earlier. Long-term steroid treatment can also lead to osteoporosis.

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 sodium 5 mg is used:
- to reduce the risk of vertebral fractures in women with postmenopausal osteoporosis. It also reduces the risk of hip fractures in women with established postmenopausal osteoporosis.
- to prevent osteoporosis in postmenopausal women with an increased risk of osteoporosis.
- to maintain or increase bone mass in postmenopausal women who have been on high doses of steroids drugs for a long time.

2. BEFORE YOU TAKE RISEDRONATE SODIUM 5 MG

Do not take Risedronate sodium 5 mg

- If you are allergic to risedronate sodium or any of the other ingredients of Risedronate sodium 5 mg (see section 6, “What Risedronate sodium 5 mg contains”)
- If your doctor has told you that you have a condition called hypocalcaemia (a low blood calcium level)
- If you may be pregnant, are pregnant or planning to become pregnant
- If you are breast-feeding
- If you have severe kidney problems.

Take special care and talk to your doctor before you start taking Risedronate sodium 5 mg

- If you are unable to stay in an upright position (sitting or standing) for at least 30 minutes.
- If you have abnormal bone and mineral metabolism (for example lack of vitamin D, parathyroid hormone abnormalities, both leading to a low blood calcium level).
- If you have had problems in the past with your oesophagus (the tube that connects your mouth with your stomach). For instance you may have had pain or difficulty in swallowing food.
- If you have been told by your doctor that you have an intolerance to some sugars (such as lactose).
- If you have or ever had pain, swelling or numbness of the jaw or a “heavy jaw feeling” or loosening of a tooth.
- If you are under dental treatment or will undergo dental surgery, tell your dentist that you are being treated with Risedronate sodium 5 mg.

Your doctor will advise you on what to do when taking Risedronate sodium 5 mg if you have any of the above.

Taking other medicines

Medicines containing one of the following lessen the effect of Risedronate sodium 5 mg if taken at the same time:

- calcium
- magnesium
- aluminium (for example some indigestion mixtures)
- iron.

Take these medicines at least 30 minutes after your Risedronate sodium 5 mg tablet.

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.
**Taking Risedronate sodium 5 mg with food and drink**
It is very important that you do not take your Risedronate sodium 5 mg tablet with food or drinks (other than plain water) so that it can work properly. Products containing one of the following: calcium (including dairy products such as milk), magnesium, aluminium (for example, some indigestion mixtures) or iron lessen the effect of this medicine.
These products should be taken at a different time of Risedronate sodium 5 mg tablets.

**Pregnancy and breast-feeding**
Do not take Risedronate sodium 5 mg if you may be pregnant, are pregnant or planning to become pregnant (see section 2, “Do not take Risedronate sodium 5 mg”). The potential risk associated with the use of risedronate sodium in pregnant women is unknown.
Do not take Risedronate sodium 5 mg if you are breast-feeding. (see section 2, “Do not take Risedronate sodium 5 mg”).

Risedronate sodium 5 mg should only be used to treat postmenopausal women.

**Driving and using machines**
Risedronate sodium 5 mg is not known to affect your ability to drive and use machines.

**Important information about some of the ingredients of Risedronate sodium 5 mg**
Risedronate sodium 5 mg contains a small amount of lactose.
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking Risedronate sodium 5 mg.

**3. HOW TO TAKE RISEDRONATE SODIUM 5 MG**

**Dosage**
Always take Risedronate sodium 5 mg exactly as your doctor has told you. You should check with your doctor if you are not sure.

**Usual dose:**
Take one Risedronate sodium 5 mg tablet once a day.
It is very important that you do not take Risedronate sodium 5 mg with food or drinks (other than plain water) so that it can work properly.

**When to take the Risedronate sodium 5 mg**
It is best to take your tablet at least 30 minutes before the first food, drink (other than plain water) or other medicine of the day.
If you are unable to take your Risedronate sodium 5 mg tablet at this time, you may take it on an empty stomach, at the same time every day, in one of the following ways:
- Between meals: at least 2 hours after your last food, drink (other than plain water) or medicine. Do not eat or drink (other than plain water) for 2 hours after taking the tablet.
- In the evening: at least 2 hours after the last food, drink (other than plain water) or medicine of the day. Risedronate sodium 5 mg should be taken at least 30 minutes before going to bed.

**How to take the Risedronate sodium 5 mg**
- Take the tablet whilst you are in an upright position (you may sit or stand) to avoid heartburn.
- Swallow it with at least one glass (120 ml) of plain water.
- Swallow it whole. Do not suck or chew it.
- Do not lie down for 30 minutes after taking your tablet.

Your doctor will tell you if you need calcium and vitamin supplements, if you are not taking enough from your diet.

**If you take more Risedronate sodium 5 mg than you should**
If you or somebody else has accidentally taken more Risedronate sodium 5 mg tablet than prescribed, drink one full glass of milk and seek medical attention.

**If you forget to take Risedronate sodium 5 mg**
If you have forgotten to take your tablet, you can take it before breakfast, between meals, or in the evening according to the instructions above.

Do not take two tablets in one day to make up for the tablet you missed.

**If you stop taking Risedronate sodium 5 mg**
If you stop treatment you may begin to lose bone mass. Please talk to your doctor before you consider stopping treatment.

**4. POSSIBLE SIDE EFFECTS**

Like all medicines, Risedronate sodium 5 mg can cause side effects, although not everybody gets them.

**Stop taking Risedronate sodium 5 mg and contact a doctor immediately** if you experience any of the following:
- Symptoms characteristics of severe tissue swelling (angioedema reaction)
  - Swelling of face, tongue or throat
  - Difficulties in swallowing
  - Hives and difficulties in breathing
- Severe skin reactions that can include blistering of the skin.

**Tell your doctor promptly** if you experience the following side effects:
- Eye inflammation, usually with pain, redness and light sensitivity.
• Bone necrosis of the jaw (osteonecrosis) associated with delayed healing and infection, often following tooth extraction (see section 2, “Take special care and talk to your doctor before you start taking Risedronate sodium 5 mg”).
• Symptoms from oesophagus such as pain when you swallow, difficulties in swallowing, chest pain or new or worsened heartburn.

However in clinical studies the other side effects that were observed were usually mild and did not cause the patient to stop taking their tablets.

**Common side effects** (affects 1 to 10 users in 100)
• Indigestion, feeling sick, stomach ache, stomach cramps or discomfort, constipation, feelings of fullness, bloating, diarrhoea.
• Pain in your bones, muscles or joints.
• Headache.

**Uncommon side effects** (affects 1 to 10 users in 1000)
• Inflammation or ulcer of the oesophagus (the tube that connects your mouth with your stomach) causing difficulty and pain in swallowing (see also section 2, “Take special care and talk to your doctor before you start taking Risedronate sodium 5 mg”), inflammation of the stomach and duodenum (bowel draining the stomach).
• Inflammation of the coloured part of the eye (iris) (red painful eyes with a possible change in vision).

**Rare side effects** (affects 1 to 10 users in 10000)
• Inflammation of the tongue (red swollen, possibly painful), narrowing of the oesophagus (the tube that connects your mouth with your stomach).
• Abnormal liver tests have been reported. These can only be diagnosed from a blood test.

During post-marketing experience, the following have been reported (unknown frequency):
• Hair loss.
• Liver disorders, some cases were severe.

Rarely, at the beginning of treatment, a patient’s blood calcium and phosphate levels may fall. These changes are usually small and cause no symptoms.

If any of the side effects becomes severe, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

### 5. HOW TO STORE RISETRONATE SODIUM 5 MG

Keep out of the reach and sight of children.
Do not use this medicine after the expiry date which is stated on the pack after EXP. The expiry date refers to the last day of that month.
No special storage condition required.
Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help protect the environment.

6. FURTHER INFORMATION

What Risedronate sodium 5 mg contains
The active substance is risedronate sodium. Each tablet contains 5 mg risedronate sodium, equivalent to 4.64 mg risedronic acid.

The other ingredients are:
*Tablet core:* lactose monohydrate, crospovidone, magnesium stearate and microcrystalline cellulose.

*Film coating:* hypromellose, titanium dioxide (E171), macrogol, hydroxypropyl cellulose, iron oxide yellow (E172) and colloidal anhydrous silica.

What Risedronate sodium 5 mg looks like and contents of the pack
Risedronate sodium 5 mg film-coated tablets are light-yellow coloured tablets debossed with the letter “J” on one side and “5” on the other.
The tablets are supplied in blister packs of 14, 20, 28, 30, 84 or 98 tablets. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
*Marketing Authorisation Holder:*
Waymade Healthcare Plc trading as Sovereign Medical
Sovereign House
Miles Gray Road
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*Manufacturer:*
PSI supply nv
Axxes Business Park
Guldensporenpark 22 – Block C
9820 Merelbeke
Belgium

Waymade Healthcare Plc
Sovereign House
Miles Gray Road
Basildon
Essex, SS14 3FR
United Kingdom

This leaflet was last approved in
Risedronate sodium 30 mg film-coated tablets

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects becomes severe, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Risedronate sodium 30 mg is and what it is used for
2. Before you take Risedronate sodium 30 mg
3. How to take Risedronate sodium 30 mg
4. Possible side effects
5. How to store Risedronate sodium 30 mg
6. Further information

1. WHAT RISEDRONATE SODIUM 30 MG IS AND WHAT IT IS USED FOR

Risedronate sodium 30 mg belongs to a group of non-hormonal medicines called bisphosphonates which are used to treat bone diseases.
Risedronate sodium 30 mg is used to treat Paget’s disease of the bone.

Bone is a living tissue. Old bone is constantly removed from your skeleton and replaced with new bone. Paget’s disease occurs when this process, called remodeling, happens too quickly and in a disordered way. The new bone that is produced is weaker than normal and the affected bones may become enlarged, painful and may fracture. Risedronate sodium 30 mg changes the bone remodeling process back to normal, returning the strength to the bone structure.

2. BEFORE YOU TAKE RISEDRONATE SODIUM 30 MG

Do not take Risedronate sodium 30 mg
- If you are allergic to risedronate sodium or any of the other ingredients of Risedronate sodium 30 mg (see section 6, “What Risedronate sodium 30 mg contains”)
- If your doctor has told you that you have a condition called hypocalcaemia (a low blood calcium level)
- If you may be pregnant, are pregnant or planning to become pregnant
- If you are breast-feeding
- If you have severe kidney problems.

Take special care and talk to your doctor before you start taking Risedronate sodium 30 mg
- If you are unable to stay in an upright position (sitting or standing) for at least 30 minutes.
- If you have abnormal bone and mineral metabolism (for example lack of vitamin D, parathyroid hormone abnormalities, both leading to a low blood calcium level).
- If you have had problems in the past with your oesophagus (the tube that connects your mouth with your stomach). For instance you may have had pain or difficulty in swallowing food.
- If you have been told by your doctor that you have an intolerance to some sugars (such as lactose).
- If you have or ever had pain, swelling or numbness of the jaw or a “heavy jaw feeling” or loosening of a tooth.
- If you are under dental treatment or will undergo dental surgery, tell your dentist that you are being treated with Risedronate sodium 30 mg.

Your doctor will advise you on what to do when taking Risedronate sodium 30 mg if you have any of the above.

Taking other medicines
Medicines containing one of the following lessen the effect of Risedronate sodium 30 mg if taken at the same time:
- calcium
- magnesium
- aluminium (for example some indigestion mixtures)
- iron.

Take these medicines at least 30 minutes after your Risedronate sodium 30 mg tablet.
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

**Taking Risedronate sodium 30 mg with food and drink**

It is very important that you **do not** take your Risedronate sodium 30 mg tablet with food or drinks (other than plain water) so that it can work properly. Products containing one of the following: calcium (including dairy products such as milk), magnesium, aluminium (for example, some indigestion mixtures) or iron lessen the effect of this medicine.

These products should be taken at a different time of Risedronate sodium 30 mg tablets.

**Pregnancy and breast-feeding**

**Do not** take Risedronate sodium 30 mg if you may be pregnant, are pregnant or planning to become pregnant (see section 2, “Do not take Risedronate sodium 30 mg”). The potential risk associated with the use of risedronate sodium in pregnant women is unknown.

**Do not** take Risedronate sodium 30 mg if you are breast-feeding. (see section 2, “Do not take Risedronate sodium 30 mg”).

Ask your doctor for advice before taking any medicine.

**Driving and using machines**

Risedronate sodium 30 mg is not known to affect your ability to drive and use machines.

**Important information about some of the ingredients of Risedronate sodium 30 mg**

Risedronate sodium 30 mg contains a small amount of lactose.

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking Risedronate sodium 30 mg.

**3. HOW TO TAKE RISEDRONATE SODIUM 30 MG**

**Dosage**

Always take Risedronate sodium 30 mg exactly as your doctor has told you. You should check with your doctor if you are not sure.

**Usual dose:**

Take one Risedronate sodium 30 mg tablet once a day.

Usually 2 months will be enough to treat your Paget’s disease. However, another course of treatment may be required.

It is very important that you **do not** take Risedronate sodium 30 mg with food or drinks (other than plain water) so that it can work properly.

**When to take the Risedronate sodium 30 mg**

It is best to take your tablet at least 30 minutes before the first food, drink (other than plain water) or other medicine of the day.

If you are unable to take your Risedronate sodium 30 mg tablet at this time, you may take it on an empty stomach, at the same time every day, in one of the following ways:

- Between meals: at least 2 hours after your last food, drink (other than plain water) or medicine. Do not eat or drink (other than plain water) for 2 hours after taking the tablet.
- In the evening: at least 2 hours after the last food, drink (other than plain water) or medicine of the day. Risedronate sodium 30 mg should be taken at least 30 minutes before going to bed.

**How to take the Risedronate sodium 30 mg**

- Take the tablet whilst you are in an upright position (you may sit or stand) to avoid heartburn.
- Swallow it with at least one glass (120 ml) of plain water.
- Swallow it whole. Do not suck or chew it. Do not lie down for 30 minutes after taking your tablet.

Your doctor will tell you if you need calcium and vitamin supplements, if you are not taking enough from your diet.

**If you take more Risedronate sodium 30 mg than you should**

If you or somebody else has accidentally taken more Risedronate sodium 30 mg tablets than prescribed, drink one full glass of milk and seek medical attention.

**If you forget to take Risedronate sodium 30 mg**

If you have forgotten to take your tablet, you can take it before breakfast, between meals, or in the evening according to the instructions above.

Do not take two tablets in one day to make up for the tablet you missed.
If you stop taking Risedronate sodium 30 mg Do not stop the treatment prematurely because Paget’s disease is a long-term disease. Please talk to your doctor before you consider stopping treatment.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Risedronate sodium 30 mg can cause side effects, although not everybody gets them.

Stop taking Risedronate sodium 30 mg and contact a doctor immediately if you experience any of the following:
- Symptoms characteristics of severe tissue swelling (angioedema reaction)
- Swelling of face, tongue or throat
- Difficulties in swallowing
- Hives and difficulties in breathing
- Severe skin reactions that can include blistering of the skin.

Tell your doctor promptly if you experience the following side effects:
- Eye inflammation, usually with pain, redness and light sensitivity.
- Bone necrosis of the jaw (osteonecrosis) associated with delayed healing and infection, often following tooth extraction (see section 2, “Take special care and talk to your doctor before you start taking Risedronate sodium 30 mg”).
- Symptoms from oesophagus such as pain when you swallow, difficulties in swallowing, chest pain or new or worsened heartburn.

However in clinical studies the other side effects that were observed were usually mild and did not cause the patient to stop taking their tablets.

Common side effects (affects 1 to 10 users in 100)
- Indigestion, feeling sick, stomach ache, stomach cramps or discomfort, constipation, feelings of fullness, bloating, diarrhoea.
- Pain in your bones, muscles or joints.
- Headache.

Uncommon side effects (affects 1 to 10 users in 1,000)
- Inflammation or ulcer of the oesophagus (the tube that connects your mouth with your stomach) causing difficulty and pain in swallowing (see also section 2, “Take special care and talk to your doctor before you start taking Risedronate sodium 30 mg”), inflammation of the stomach and duodenum (bowel draining the stomach).
- Inflammation of the coloured part of the eye (iris) (red painful eyes with a possible change in vision).

Rare side effects (affects 1 to 10 users in 10,000)
- Inflammation of the tongue (red swollen, possibly painful), narrowing of the oesophagus (the tube that connects your mouth with your stomach).
- Abnormal liver tests have been reported. These can only be diagnosed from a blood test.

During post-marketing experience, the following have been reported (unknown frequency):
- Hair loss.
- Liver disorders, some cases were severe.

Rarely, at the beginning of treatment, a patient’s blood calcium and phosphate levels may fall. These changes are usually small and cause no symptoms. The additional following adverse events have also been observed in a clinical study in patients with Paget’s disease: vision difficulties, breathing difficulties, coughing, inflammation of the large intestine, surface of the eye damage, cramps, dizziness, dryness of the eye, flu-like symptoms, muscle weakness, abnormal growth of cells, a frequent need to pass water at night, unusual lumps or swellings, chest pain, rash, runny nose, ringing in the ears and weight loss.

If any of the side effects becomes severe, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.
5. HOW TO STORE RISEDRONATE SODIUM 30 MG

Keep out of the reach and sight of children.
Do not use this medicine after the expiry date which is stated on the pack after EXP. The expiry date refers to the last day of that month.

No special storage condition required.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Risedronate sodium 30 mg contains
The active substance is risedronate sodium. Each tablet contains 30 mg risedronate sodium, equivalent to 27.8 mg risedronic acid.

The other ingredients are:
*Tablet core:* lactose monohydrate, crospovidone, magnesium stearate and microcrystalline cellulose.

*Film coating:* hypromellose, macrogol, hydroxypropyl cellulose, colloidal anhydrous silica and titanium dioxide (E171).

What Risedronate sodium 30 mg looks like and contents of the pack
Risedronate sodium 30 mg film-coated tablets are white to off-white coloured tablets debossed with the letter “J” on one side and “30” on the other. The tablets are supplied in blister packs of 28 or 30 tablets. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
*Marketing Authorisation Holder:* Waymade Healthcare Plc trading as Sovereign Medical
Sovereign House
Miles Gray Road
Basildon
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United Kingdom

This leaflet was last approved in
Risedronate sodium 35 mg film-coated tablets

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects becomes severe, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Risedronate sodium 35 mg is and what it is used for
2. Before you take Risedronate sodium 35 mg
3. How to take Risedronate sodium 35 mg
4. Possible side effects
5. How to store Risedronate sodium 35 mg
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1. WHAT RISEDRONATE SODIUM 35 MG IS AND WHAT IT IS USED FOR

Risedronate sodium 35 mg 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 sodium 35 mg is used for the treatment of osteoporosis:
- in postmenopausal women, even if osteoporosis is severe. It reduces the risk of spinal and hip fractures.
- in men.

2. BEFORE YOU TAKE RISEDRONATE SODIUM 35 MG

Do not take Risedronate sodium 35 mg

- If you are allergic to risedronate sodium or any of the other ingredients of Risedronate sodium 35 mg (see section 6, “What Risedronate sodium 35 mg contains”)
- If your doctor has told you that you have a condition called hypocalcaemia (a low blood calcium level)
- If you may be pregnant, are pregnant or planning to become pregnant
- If you are breast-feeding
- If you have severe kidney problems.

Take special care and talk to your doctor before you start taking Risedronate sodium 35 mg

- If you are unable to stay in an upright position (sitting or standing) for at least 30 minutes.
• If you have abnormal bone and mineral metabolism (for example lack of vitamin D, parathyroid hormone abnormalities, both leading to a low blood calcium level).
• If you have had problems in the past with your oesophagus (the tube that connects your mouth with your stomach). For instance you may have had pain or difficulty in swallowing food.
• If you have been told by your doctor that you have an intolerance to some sugars (such as lactose).
• If you have had or have pain, swelling or numbness of the jaw or a “heavy jaw feeling” or loosening of a tooth.
• If you are under dental treatment or will undergo dental surgery, tell your dentist that you are being treated with Risedronate sodium 35 mg.

Your doctor will advise you on what to do when taking Risedronate sodium 35 mg if you have any of the above.

Taking other medicines
Medicines containing one of the following lessen the effect of Risedronate sodium 35 mg if taken at the same time:
• calcium
• magnesium
• aluminium (for example some indigestion mixtures)
• iron.

Take these medicines at least 30 minutes after your Risedronate sodium 35 mg tablet.

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Taking Risedronate sodium 35 mg with food and drink
It is very important that you do not take your Risedronate sodium 35 mg tablet with food or drinks (other than plain water) so that it can work properly. In particular do not take this medicine at the same time as dairy products (such as milk) as they contain calcium (see section 2, “Taking other medicines”). Take food and drinks (other than plain water) at least 30 minutes after your Risedronate sodium 35 mg tablet.

Pregnancy and breast-feeding
Do not take Risedronate sodium 35 mg if you may be pregnant, are pregnant or planning to become pregnant (see section 2, “Do not take Risedronate sodium 35 mg”). The potential risk associated with the use of risedronate sodium in pregnant women is unknown.

Do not take Risedronate sodium 35 mg if you are breast-feeding. (see section 2, “Do not take Risedronate sodium 35 mg”).

Risedronate sodium 35 mg should only be used to treat postmenopausal women and men.

Driving and using machines
Risedronate sodium 35 mg is not known to affect your ability to drive and use machines.

Important information about some of the ingredients of Risedronate sodium 35 mg
Risedronate sodium 35 mg contains a small amount of lactose.
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking Risedronate sodium 35 mg.
3. HOW TO TAKE RISEDRONATE SODIUM 35 MG

Dosage
Always take Risedronate sodium 35 mg exactly as your doctor has told you. You should check with your doctor if you are not sure.

Usual dose:
Take one Risedronate sodium 35 mg tablet once a week.
Choose one day of the week that best fits your schedule. Every week, take the Risedronate sodium 35 mg tablet on your chosen day.

When to take the Risedronate sodium 35 mg
Take your Risedronate sodium 35 mg tablet at least 30 minutes before the first food, drink (other than plain water) or other medicine of the day.

How to take the Risedronate sodium 35 mg
- Take the tablet whilst you are in an upright position (you may sit or stand) to avoid heartburn.
- Swallow it with at least one glass (120 ml) of plain water.
- Swallow it whole. Do not suck or chew it.
- Do not lie down for 30 minutes after taking your tablet.

Your doctor will tell you if you need calcium and vitamin supplements, if you are not taking enough from your diet.

If you take more Risedronate sodium 35 mg than you should
If you or somebody else has accidentally taken more Risedronate sodium 35 mg tablets than prescribed, drink one full glass of milk and seek medical attention.

If you forget to take Risedronate sodium 35 mg
If you have forgotten to take your tablet on your chosen day, take it on the day you remember. Return to taking one tablet once a week on the day the tablet is normally taken.

Do not take two tablets in one day to make up for the tablet you missed.

If you stop taking Risedronate sodium 35 mg
If you stop treatment you may begin to lose bone mass. Please talk to your doctor before you consider stopping treatment.

4. POSSIBLE SIDE EFFECTS
Like all medicines, Risedronate sodium 35 mg can cause side effects, although not everybody gets them.

Stop taking Risedronate sodium 35 mg and contact a doctor immediately if you experience any of the following:
- Symptoms characteristics of severe tissue swelling (angioedema reaction)
  - Swelling of face, tongue or throat
  - Difficulties in swallowing
  - Hives and difficulties in breathing
- Severe skin reactions that can include blistering of the skin.

Tell your doctor promptly if you experience the following side effects:
- Eye inflammation, usually with pain, redness and light sensitivity.
- Bone necrosis of the jaw (osteonecrosis) associated with delayed healing and infection, often following tooth extraction (see section 2, “Take special care and talk to your doctor before you start taking Risedronate sodium 35 mg”).
- Symptoms from oesophagus such as pain when you swallow, difficulties in swallowing, chest pain or new or worsened heartburn.
However in clinical studies the other side effects that were observed were usually mild and did not cause the patient to stop taking their tablets.

**Common side effects**
(affects 1 to 10 users in 100)
- Indigestion, feeling sick, stomach ache, stomach cramps or discomfort, constipation, feelings of fullness, bloating, diarrhoea.
- Pain in your bones, muscles or joints.
- Headache.

**Uncommon side effects**
(affects 1 to 10 users in 1000)
- Inflammation or ulcer of the oesophagus (the tube that connects your mouth with your stomach) causing difficulty and pain in swallowing (see also section 2. "Take special care and talk to your doctor before you start taking Risedronate sodium 35 mg").
- Inflammation of the stomach and duodenum (bowel draining the stomach).
- Inflammation of the coloured part of the eye (iris) (red painful eyes with a possible change in vision).

**Rare side effects**
(affects 1 to 10 users in 10,000)
- Inflammation of the tongue (red swollen, possibly painful), narrowing of the oesophagus (the tube that connects your mouth with your stomach).
- Abnormal liver tests have been reported. These can only be diagnosed from a blood test.

During post-marketing experience, the following have been reported (unknown frequency):
- Hair loss.
- Liver disorders, some cases were severe.

5. **HOW TO STORE RISEDRONATE SODIUM 35 MG**

Keep out of the reach and sight of children. Do not use this medicine after the expiry date which is stated on the pack after EXP. The expiry date refers to the last day of that month.

No special storage condition required.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. **FURTHER INFORMATION**

**What Risedronate sodium 35 mg contains**
The active substance is risedronate sodium. Each tablet contains 35 mg risedronate sodium, equivalent to 32.5 mg risedronic acid.

The other ingredients are:
- **Tablet core**: lactose monohydrate, croscarmellose sodium, magnesium stearate and microcrystalline cellulose.
- **Film coating**: iron oxide yellow (E172), iron oxide red (E172), hypromellose, macrogol, hydroxypropyl cellulose, colloidal amorphous silica and titanium dioxide (E171).

**What Risedronate sodium 35 mg looks like and contents of the pack**
Risedronate sodium 35 mg film-coated tablets are light-orange coloured tablets debossed with the letter “J” on one side and “35” on the other.

The tablets are supplied in blister packs of 4 or 12 tablets. Not all pack sizes may be marketed.
Risedronate sodium 5 mg film-coated tablets
28 film-coated tablets

Each film-coated tablet contains 5 mg risedronate sodium (equivalent to 4.64 mg risedronic acid). Contains lactose monohydrate.

No special storage condition required. KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.

Use as directed by a doctor.
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