Public Assessment Report

Decentralised Procedure

RISEDRONATE SODIUM 35MG TABLETS

UK/H/1936/001/DC
UK Licence No: PL 17640/0027

BETAPHARM ARZNEIMITTEL GMBH
LAY SUMMARY

On 27th October 2010, the UK granted Betapharm Arzneimittel GmbH a Marketing Authorisation (licence) for Risedronate Sodium 35mg Tablets (PL 17640/0027; UK/H/1936/001/DC).

The active ingredient in this medicine is risedronate sodium.

Risedronate sodium belongs to a group of non-hormonal medicines known as bisphosphonates, which prevent bone loss from the body. Risedronate sodium is used to treat a condition called osteoporosis (brittle bones) in postmenopausal women and men.

Risedronate sodium helps to prevent bone loss and to build up bone which may have been lost due to osteoporosis. It can therefore reduce the risk of back and hip fractures.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Risedronate Sodium 35mg Tablets outweigh the risks; hence this Marketing Authorisation has been granted.
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| Module 6: Steps taken after initial procedure | Not applicable |
### Module 1

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<td>Generic application, Article 10.1</td>
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<td><strong>Strength</strong></td>
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<td><strong>MA Holder</strong></td>
<td>Betapharm Arzneimittel GmbH</td>
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<tr>
<td></td>
<td>Kobelweg 95</td>
</tr>
<tr>
<td></td>
<td>86156 Augsburg</td>
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<td></td>
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<td><strong>Reference Member State (RMS)</strong></td>
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</tr>
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Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Risedronate Sodium 35mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 35 mg risedronate sodium (equivalent to 32.5 mg risedronic acid).

Excipient(s):
Each tablet contains 93 mg sorbitol.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Tablet
White to off white capsule shaped tablet with ‘D’ on one side and ‘RE 35’ on the other side

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
Posology
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 35 mg tablets:

- 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 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.

Method of Administration
The tablet must be swallowed whole and not sucked or chewed. To aid delivery of the tablet to the stomach Risedronate 35 mg tablet 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).

Paediatric population: Risedronate sodium is not recommended for use in children below age 18 due to insufficient data on safety and efficacy (also see section 5.1).
4.3 Contraindications
Hypersensitivity to risedronate sodium or to any of its excipients.
Hypocalcaemia (see section 4.4).
Pregnancy and lactation (see section 4.6).
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 35 mg tablets (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 35 mg tablet therapy. Other disturbances of bone and mineral metabolism (i.e. parathyroid dysfunction, hypovitaminosis D) should be treated at the time of starting Risedronate 35 mg tablet 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 sorbitol. Patients with rare hereditary problems of fructose intolerance 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 (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

Pregnancy

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. Risedronate sodium must not be used during pregnancy.

Breastfeeding

Studies in animal indicate that a small amount of risedronate sodium pass into breast milk. Risedronate sodium must not be used by breast-feeding women.

4.7 Effects on ability to drive and use machines

Risedronate sodium has no or negligible influence on the ability to drive and use machines.

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 (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <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, bullous skin reactions and leukocytoclastic vasculitis, 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.

Respiratory, thoracic and mediastinal disorders:
Pneumonitis

Blood and lymphatic system disorders:
Haemolytic anaemia

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
Pharmacoco-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.

Pharmacodynamic effects
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 post-menopausal 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 35 mg tablets (once weekly) and Risedronate 5 mg tablets 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.

Clinical efficacy and safety
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 35 mg tablets (once weekly) (n=485) was shown to be equivalent to Risedronate 5 mg tablets 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 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=3661) 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. Anti-fracture efficacy was not demonstrated in this study.

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

Paediatric Population
The safety and efficacy of risedronate sodium is being investigated in an on-going study of paediatric patients aged 4 to less than 16 years with osteogenesis imperfecta. After completion of its one-year randomized, double-blind, placebo controlled phase, a statistically significant increase in lumbar spine BMD in the risedronate group versus placebo group was demonstrated; however an increased number of at least 1 new morphometric (identified by x-ray) vertebral fracture was found in the risedronate group compared to placebo. Overall, results do not support the use of risedronate sodium in paediatric patients with osteogenesis imperfecta.

5.2 Pharmacokinetic properties

Absorption: Absorption after an oral dose is relatively rapid ($t_{\text{max}}$ ~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
Microcrystalline Cellulose
Sorbitol
Colloidal Anhydrous Silica
Croscarmellose Sodium
Sodium Stearyl Fumarate

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 in order to protect from moisture.

6.5 Nature and contents of container
Aluminium/PVC-PVDC blisters in pack sizes of 1, 2, 4, 10, 12, 16 and 24 tablets as follows:

<table>
<thead>
<tr>
<th>Pack Size</th>
<th>Containing the following blisters</th>
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<tbody>
<tr>
<td>1 tablet</td>
<td>1 blister of 1 tablet</td>
</tr>
<tr>
<td>2 tablets</td>
<td>1 blister of 2 tablets</td>
</tr>
<tr>
<td>4 tablets</td>
<td>1 blister of 4 tablets</td>
</tr>
<tr>
<td>10 tablets</td>
<td>1 blister of 10 tablets</td>
</tr>
<tr>
<td>12 tablets</td>
<td>1 blister of 12 tablets or 3 blisters of 4 tablets</td>
</tr>
<tr>
<td>16 tablets</td>
<td>4 blisters of 4 tablets or 1 blister of 12 tablets and one of 4 tablets</td>
</tr>
<tr>
<td>24 tablets</td>
<td>2 blisters of 12 tablets or 2 blisters of 10 tablets and one of 4 tablets</td>
</tr>
</tbody>
</table>

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Betapharm Arzneimittel GmbH
Kobelweg 95, 86156 Augsburg
Germany
8 MARKETING AUTHORISATION NUMBER(S)
   PL 17640/0027

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
   27/10/2010

10 DATE OF REVISION OF THE TEXT
    27/10/2010
Module 3
PACKAGE LEAFLET: INFORMATION FOR THE USER

[Product Name] 35mg Tablets
(risedronate sodium)

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 further 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 get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What [Product Name] 35mg Tablets are and what they are used for
2. Before you take [Product Name] 35mg Tablets
3. How to take [Product Name] 35mg Tablets
4. Possible side effects
5. How to store [Product Name] 35mg Tablets
6. Further information

1. WHAT [PRODUCT NAME] 35MG TABLETS ARE AND WHAT THEY ARE USED FOR

Risedronate sodium belongs to a group of non-hormonal medicines known as bisphosphonates, which prevent bone loss from the body.

Risedronate sodium is used to treat a condition called osteoporosis (brittle bones) in postmenopausal women and men. This condition is common in women after the menopause. The earlier a woman reaches the menopause, the greater the risk of her developing osteoporosis.

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

Without treatment, osteoporosis can cause thinning and weakening of the bones in the skeleton which can then lead to fractures, usually of the hip, backbone and wrists. Fractures can occur easily in people suffering from osteoporosis including during normal everyday activities such as heavy lifting or from a minor injury or fall. Osteoporosis related fractures can also cause back pain, height loss and a curved back. Many patients with osteoporosis have no symptoms and may not even known that they have it.

Risedronate sodium helps to prevent bone loss and to build up bone which may have been lost due to osteoporosis. It can therefore reduce the risk of back and hip fractures.

2. BEFORE YOU TAKE [PRODUCT NAME] 35MG TABLETS

Do not take [Product Name] 35mg Tablets
- if you are allergic (hypersensitive) to risedronate sodium or any of the other ingredients of [Product Name] 35mg Tablets (which are listed in section 6. Further Information),
- if your doctor has told you that you have low calcium levels in your blood (a condition called hypocalcaemia),
- 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 with [Product Name] 35mg Tablets

Tell your doctor before taking these tablets:
- if you are unable to stay in an upright position (sitting or standing) for at least 30 minutes,
- if you have difficulty or pain when swallowing or new/worsened heartburn or chest pain,
- if you have or have had certain disorders of the oesophagus (this is also called the gullet and is the tube that connects your mouth with your stomach),
- if you have or have had problems with your stomach or upper bowel,
- if you have or have ever had low vitamin D levels,
- if you have or have had a condition called hypoparathyroidism (a condition where your parathyroid gland does not work properly),
- if you have or have had pain, swelling or numbness of the jaw, loosening of a tooth or a 'heavy jaw feeling',
- if you are undergoing dental treatment or you are to undergo dental surgery,
- if you have cancer, are undergoing chemotherapy or radiotherapy, are taking steroids or do not receive regular dental care. If so your doctor may want you to have a dental examination before starting treatment.

Children
Risedronate sodium is not recommended for use in children below age 18 due to insufficient data on safety and efficacy.

Taking other medicines
Do not take any other medicines orally (by mouth) at the same time as taking [Product Name] 35mg Tablets. You should leave at least 30 minutes between your dose of [Product Name] 35mg Tablets and any other oral medicines. It is important that you follow all of the advice given in section 3 - ‘How to take [Product Name] 35mg Tablets.’

Medicines containing one of the following reduce the effect of your medicine if taken at the same time:
- Calcium
- Magnesium
- Aluminium (for example some indigestion mixtures)
- Iron

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

Taking [Product Name] 35mg Tablets with food and drink
These tablets must be taken on an empty stomach as food and drink can greatly reduce the effectiveness of the medicine. You must take the tablets with a full glass of plain water at least 30 minutes before any other food or drink. In particular do not take this medicine at the same time as dairy products (such as milk) as they contain calcium (see section Taking other medicines). It is important that you follow all of the advice given in section 3 - ‘How to take [Product Name] 35mg Tablets.’

Pregnancy and breast-feeding
Do not take [Product Name] 35mg Tablets if you are pregnant, think you may be pregnant, planning to become pregnant or are breast-feeding.
This medicine should only be used by postmenopausal women and men.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
[Product Name] 35mg Tablets are not known to have any effects on your ability to drive and use machines.

Important information about some of the ingredients of [Product Name] 35mg Tablets
These tablets contain sorbitol. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. **HOW TO TAKE [PRODUCT NAME] 35MG TABLETS**

Always take [Product Name] 35mg Tablets exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

The usual dose is ONE [Product Name] 35mg tablet once a week.

The following instructions are particularly important to ensure that your medicine works properly and to reduce the likelihood of the medicine irritating your oesophagus (gullet):

- Choose the day of the week that best suits you to take your tablet. For your convenience to take the tablet on the correct day every week there is a feature in the blister pack. You should mark the chosen day of the week to take the tablets.
- Take one [Product Name] 35mg Tablet each week on your chosen day.
- Immediately after getting on your chosen day, take the [Product Name] 35mg Tablet on an empty stomach. It should only be taken with a full glass of plain water (not less than 120ml) and should be taken at least 30 minutes before any other food, drink or medicine. Do not take your tablet with tea, coffee, mineral water or juice.
- The tablet must be swallowed whole. You must not chew or suck the tablet or allow it to dissolve in your mouth.
- Wait at least 30 minutes after taking the tablet before you drink or eat the first meal of the day or take any other medicine (this includes calcium supplements, vitamins and antacids (which are used to treat indigestion)).
- Do not lie down after taking [Product Name] 35mg Tablets. You must stay upright (sitting, standing or walking) for at least 30 minutes after you have swallowed the tablet. It is also important that you do not lie down before you have eaten the first meal of the day.
- If you find it difficult and/or painful to swallow, or you feel pain behind the breast-bone or new or worsened heartburn, stop taking the tablets and contact your doctor.

Your doctor may also ask you to take vitamin D or calcium supplements whilst you are taking [Product Name] 35mg Tablets. If so, you should follow your doctor’s advice carefully.

[Product Name] 35mg Tablets must not be given to children.

If you take more [Product Name] 35mg Tablets than you should, drink a full glass of milk and contact your nearest doctor or hospital casualty department immediately. Do not try and make yourself sick and do not lie down.

If you forget to take [Product Name] 35mg Tablets, take one tablet on getting up the next morning after you remember. Do not take two tablets on the same day. Return to taking one tablet once a week on the day that you originally decided upon.

If you stop taking [Product Name] 35mg Tablets, your condition may deteriorate. It is important that you continue to take [Product Name] 35mg Tablets for as long as your doctor recommends. Please talk to your doctor before you consider stopping treatment.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. **POSSIBLE SIDE EFFECTS**
Like all medicines, [Product Name] 35mg Tablets can cause side effects, although not everybody gets them.

All medicines can cause allergic reactions, although serious allergic reactions are very rare. You should stop taking [Product Name] 35mg Tablets and tell your doctor immediately if you get any of the following symptoms:

- sudden wheeziness, difficulty in breathing, swelling of the eyelids, face or lips, rash or itching (especially affecting your whole body). This is known as ‘angioedema’.
- a rash, blistering or other effects on the skin, eyes, mouth or genitals, itching or high temperature (symptoms of severe skin reactions called Stevens-Johnson syndrome or toxic epidermal necrolysis).

Tell your doctor if you experience difficulty or pain when swallowing, chest pain or new/worsened heartburn. These are signs that [Product Name] 35mg Tablets are irritating your oesophagus (gullet).

To reduce the likelihood of oesophageal (gullet) reactions, indicated with an asterisk (*) below, make sure you:

- Drink a full glass of plain water with your tablet
- Stay upright (sitting, standing or walking) until you have eaten your first meal of the day. This must also be at least 30 minutes after taking your tablet.

The following side effects have been reported:

**Common side effects** (probably affecting less than 1 in 10 but more than 1 in 100 patients):
- Indigestion,
- constipation,
- pain in your bones muscles or joints,
- Feeling sick (nausea),
- diarrhoea,
- stomach ache,
- headache,

**Uncommon side effects** (probably affecting less than 1 in 100 but more than 1 in 1,000 patients):
- Inflammation of the stomach (gastritis),
- inflammation of the upper intestine (duodentitis),
- inflammation or ulcer of the oesophagus (gullet)*,
- difficulty swallowing*,
- inflammation of the coloured part of the eye (iris) (red painful eyes with a possible change in vision).

**Rare side effects** (probably affecting less than 1 in 1,000 people):
- Inflammation of the tongue (red swollen, possibly painful),
- narrowing of the oesophagus (gullet)*,
- abnormal liver tests have been reported. These can only be diagnosed from a blood test.

The following side effects have also been reported (unknown frequency):
- Inflammation of the eye,
- pain, swelling or numbness of the jaw, loosening of a tooth or a 'heavy jaw feeling',
- hair loss,
- liver disorders, some cases were severe
- a decrease in blood calcium and phosphate levels (these changes are usually small and cause no symptoms)
- Anaemia (feeling tired)
- Inflammation of the lungs (breathless)
- Inflammation of small blood vessels.
PAR Risedronate Sodium 35mg Tablets   UK/H/1936/001/DC

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

5. **HOW TO STORE [PRODUCT NAME] 35MG TABLETS**

*Keep out of the reach and sight of children.*

Do not use your medicine after the expiry date which is stated on the carton after EXP. The expiry date refers to the last day of that month.

Do not store above 25°C. Store in the original package in order to protect from moisture.

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 [Product Name] 35mg Tablets contains**

The active substance is risedronate sodium. Each tablet contains 35 mg risedronate sodium which is equivalent to 32.5 mg risedronic acid.

The other ingredients are microcrystalline cellulose, sorbitol, colloidal anhydrous silica, croscarmellose sodium and sodium stearyl fumarate.

**What [Product Name] 35mg Tablets looks like and contents of the pack**

[Product Name] 35mg Tablets are white to off white capsule shaped tablet with ‘D’ on one side and ‘RE 35’ on the other side.

The tablets are available in blister packs of 1, 2, 4, 10, 12, 16 and 24 tablets.

Not all pack sizes may be marketed.

**Marketing Authorisation Holder**

[To be completed nationally]

**Manufacturer**

{Name and address}
<br/>{tel}
<br/>{fax}
<br/>{e-mail}

This medicinal product is authorised in the Member States of the EEA under the following names:

[To be completed nationally]

This leaflet was last approved in {MM/YYYY}.

[To be completed nationally]
Module 4
Labelling

PARTICULARS TO APPEAR ON THE OUTER PACKAGING CARTON

1. NAME OF THE MEDICINAL PRODUCT

[To be completed Nationally]

(risedronate sodium)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 35 mg riseredonate sodium (equivalent to 32.5 mg risedronic acid).

3. LIST OF EXCIPIENTS

These tablets contain sorbitol.

4. PHARMACEUTICAL FORM AND CONTENTS

1 tablet
2 tablets
4 tablets
10 tablets
12 tablets
16 tablets
24 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

[Not applicable]

8. EXPIRY DATE

EXP: (MM/YYYY)
9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C. Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

[Not applicable]

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

BN:

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

[Not applicable]

16. INFORMATION IN BRAILLE

[To be completed nationally]
<table>
<thead>
<tr>
<th>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BLISTERS</strong></td>
</tr>
</tbody>
</table>

1. **NAME OF THE MEDICINAL PRODUCT**

[To be completed Nationally]

(risedronate sodium)

2. **NAME OF THE MARKETING AUTHORISATION HOLDER**

[To be completed nationally]

3. **EXPIRY DATE**

EXP: {MM/YYYY}

4. **BATCH NUMBER**

BN:

5. **OTHER**

Mark the day of the week that suits you best

MON TUE WED THU FRI SAT SUN
Module 5
Scientific discussion during initial procedure

I  INTRODUCTION
Based on the review of the data on quality, safety and efficacy, Germany and the UK considered that the application for Risedronate Sodium 35mg Tablets could be approved. This product is a prescription only medicine (POM) indicated for the treatment of:
- Postmenopausal osteoporosis, to reduce the risk of vertebral fractures.
- Established postmenopausal osteoporosis, to reduce the risk of hip fractures.
- Osteoporosis in men at high risk of fractures.

This application for Risedronate Sodium 35mg Tablets was submitted according to Article 10.1 of Directive 2001/83/EC, claiming to be a generic medicinal product of Fortipan 30mg Film-coated tablets which was granted in the EEA on 7th October 1999 to Proctor & Gamble Pharmaceuticals Limited.

The UK reference product is Actonel Once a Week 35mg film-coated tablets which was granted in the UK on 13th January 2003 to Warner Chilcott Pharmaceuticals UK Limited.

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.

No new non-clinical studies were conducted, which is acceptable given that the product contains a widely-used, well-known active substance. No clinical studies, with the exception of the bioequivalence study, have been performed and none are required for this application as the pharmacology of risedronate sodium is well-established.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

The RMS considers that the pharmacovigilance system as described by the applicant fulfils the requirements and 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 either in the Community or in a third country.

A satisfactory justification has been provided for non-submission of a Risk Management Plan has been provided.
II. ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Risedronate Sodium 35mg Tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Risedronate Sodium</td>
</tr>
<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Bisphosphonates (M05BA07)</td>
</tr>
<tr>
<td>Pharmaceutical form and strength(s)</td>
<td>35mg tablets</td>
</tr>
<tr>
<td>Reference numbers for the Decentralised Procedure</td>
<td>UK/H/1936/001/DC</td>
</tr>
<tr>
<td>Reference Member State</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>Member States concerned</td>
<td>Germany (DE)</td>
</tr>
<tr>
<td>Marketing Authorisation Number(s)</td>
<td>PL 17640/0027</td>
</tr>
<tr>
<td>Name and address of the authorisation holder</td>
<td>Betapharm Arzneimittel GmbH</td>
</tr>
<tr>
<td></td>
<td>Kobelweg 95</td>
</tr>
<tr>
<td></td>
<td>86156 Augsburg</td>
</tr>
<tr>
<td></td>
<td>Germany</td>
</tr>
</tbody>
</table>
III SCIENTIFIC OVERVIEW AND DISCUSSION
III.1 QUALITY ASPECTS

S. Active substance

INN/Ph.Eur name: Risedronate Sodium

Chemical name:
- [1-Hydroxy-2-(3-pyridinyl) ethylidene] biphosphonic acid sodium salt.

Structural formula:

![Structural formula of Risedronate Sodium]

Molecular formula: C_{7}H_{10}NNaO_{7}P_{2}

Appearance: A white to off-white powder.

Molecular weight: 305.09

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 ingredient.

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.

P. Medicinal Product

Other Ingredients

Other ingredients inside the tablet core consist of pharmaceutical excipients microcrystalline cellulose, sorbitol, colloidal anhydrous silica, croscarmellose sodium and sodium stearyl fumarate.

All excipients comply with their respective European Pharmacopoeia monographs.
None of the excipients used contain material of animal or human origin.

No genetically modified organisms (GMO) have been used in the preparation of this product.

**Pharmaceutical Development**
The objective of the development programme was to produce a safe, efficacious product containing risedronate sodium that could be considered a generic medicinal product of Actonel Once a Week 35mg film-coated tablets which was granted in the UK on 13th January 2003 to Warner Chilcott Pharmaceuticals UK Limited.

The applicant has provided suitable product development sections. 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 reference product.

The reference product used in the bioequivalence study is Actonel 35mg tablets, licensed in Germany. This product is considered to be equivalent to the UK reference product.

**Manufacturing Process**
A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. Process validation data on pilot-scale batches have been provided. The results are satisfactory. The applicant has committed to perform process validation on future production-scale batches.

**Finished Product Specification**
The finished product specification is acceptable. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

**Container-Closure System**
These products are packaged in blisters composed of aluminium, polyvinyl chloride (PVC) and polyvinylidene chloride (PVdC).

The product comes in pack sizes of 1, 2, 4, 10, 12, 16 and 24 tablets.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary product packaging complies with EU legislation regarding contact with food.

**Stability of the product**
Stability studies were performed on batches of the finished products in the packaging proposed for marketing and in accordance with current guidelines. These data support a shelf-life of 2 years with storage instructions ‘Do not store above 25°C’ and ‘Store in the original package in order to protect from moisture’.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels**
The SmPC, PIL and labelling are pharmaceutically acceptable. The UK PIL and label mock-ups are included in modules 3 and 4 of this report.
User testing results have been submitted for the PIL for this product. The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that they contain.

**MAA forms**
The MAA form is pharmaceutically satisfactory.

**Expert report**
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

**Conclusion**
It is recommended that a Marketing Authorisation is granted for this application.
III.2 NON-CLINICAL ASPECTS

The pharmacodynamics, pharmacokinetics and toxicological properties of risedronate sodium are well-known. As risedronate sodium is widely used, well-known active substance, the applicant has not provided any new non-clinical data and none are required.

The non-clinical expert report has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

A satisfactory justification has been provided for non-submission of an Environmental Risk Assessment.

It is recommended that a Marketing Authorisation is granted for this application.
III.3 CLINICAL ASPECTS
CLINICAL PHARMACOLOGY

With the exception of the following bioequivalence study, no new pharmacokinetic or pharmacodynamic data were submitted with this application and none were required.

Pharmacokinetics
A single-dose, open-label, randomised, two-way, crossover study to compare the pharmacokinetics of the test product Risedronate Sodium 35mg tablets versus the reference product Actonel 35mg tablets (Proctor & Gamble Pharmaceuticals) in healthy non-smoking subjects under fasted conditions.

Blood samples were taken pre- and up to 72 hours post dose. There was a washout period of 14 days between each treatment period. Pharmacokinetic parameters were measured from the plasma and statistically analysed.

Results for risedronate sodium are presented below as log-transformed values:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC_{0-4} (ng.h/mL)</th>
<th>AUC_{0-∞} (ng.h/mL)</th>
<th>C_{max} (ng/ml)</th>
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</thead>
<tbody>
<tr>
<td>Test (T)</td>
<td>32.17</td>
<td>33.74</td>
<td>11.12</td>
</tr>
<tr>
<td>Reference (R)</td>
<td>30.30</td>
<td>32.87</td>
<td>10.19</td>
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<td></td>
<td>105.91</td>
<td>102.36</td>
<td>108.95</td>
</tr>
<tr>
<td>T/R Ratio (90% CI)</td>
<td>(94.26 – 118.99)</td>
<td>(90.80 – 115.36)</td>
<td>(96.66 – 122.81)</td>
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The results for the primary variables indicated that the 90% confidence intervals test/reference ratio of geometric means for AUC_{0-4} and C_{max} for risedronate sodium lie within acceptable limits. Thus, bioequivalence has been shown between the test and reference products in this study.

EFFICACY
No new efficacy data were submitted with this application and none were required.

SAFETY
With the exception of the data submitted during the bioequivalence study, no new safety data were submitted with this application and none were required. No new or unexpected safety concerns were raised during the bioequivalence study.

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC), PATIENT INFORMATION LEAFLET (PIL) AND LABELLING
The SmPC, PIL and labelling are medically satisfactory and consistent with those for the reference product, where appropriate.

CLINICAL EXPERT REPORT
The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

MAA FORM
The MAA Form is medically satisfactory.

CONCLUSIONS
It is recommended that a Marketing Authorisation is granted for this application.
IV  OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Risedronate Sodium 35mg 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.

NON-CLINICAL
No new non-clinical data were submitted and none are required for an application of this type.

Efficacy
Bioequivalence has been demonstrated between the applicant’s Risedronate Sodium 35mg Tablets and the reference product Actonel Once a Week 35mg film-coated tablets.

No new or unexpected safety concerns arise from this application.

The SmPC, PIL and labelling are satisfactory and consistent with that for the reference product.

BENEFIT-RISK ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. 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.
# Module 6

## STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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