NOVARTIS

Chief Medical Office & Patient Safety

# Aclasta®/Zoledronic acid 5 mg/100 mL

ZOL446

# EU Safety Risk Management Plan

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|---|---|
| Active substance (INN) | Zoledronic acid |
| Product concerned (brand name): | Aclasta |
| Document status: | Final |
| Version number: | 13.2 |
| Data lock point for this RMP | 31-Aug-2019 (clinical data)<br>31-Aug-2018 (safety data) |
| Date of final sign off | 10-Mar-2021 |



Template version 6.2 Feb 2019

**Rationale for submitting an updated RMP:**

The present Risk Management Plan (RMP) (version 13.2) has been prepared based on the second Request for Supplementary Information during the procedure EMEA/H/C/000595/II/0076 to update the summary of safety findings of the completed additional pharmacovigilance activity Study CZOL446H2422.

The previous RMP (version 13.1) has been updated to make the following changes:

- include the summary of safety findings of the completed additional pharmacovigilance activity Study CZOL446H2422

**Summary of significant changes in this RMP:**

The proposal on the changes to the list of safety concerns and missing information topics was presented based on the GVP V-Rev.2. In addition, all sections have been modified based on the new RMP template requirements.

| Part | Major changes compared to RMP v 12.1 |
|---|---|
| Part I | Updated to reflect the new template requirements. |
| Part II | **Module SI** Updated to reflect the new template requirements.<br>**Module SII** Updated to reflect the new template requirements. The safety pharmacology section was removed.<br>**Module SIII** Updated to reflect the new template requirements.<br>**Module SIV** Updated to reflect the new template requirements.<br>**Module SV** The post-marketing exposure was updated.<br>**Module SVI** Updated to reflect the new template requirements.<br>**Module SVII** Updated to include the summary of safety findings from Study CZOL446H2422.<br>**Removal of the following important identified risks:**<br>• Post-dose symptoms,<br>• Renal dysfunction,<br>• Ocular AEs,<br>• Hypocalcemia,<br>• Anaphylaxis.<br>**Removal of the following important potential risks:**<br>• Osteonecrosis outside of the jaw (AVN, fracture non-union and/or delayed union),<br>• Cerebrovascular accidents,<br>• Atrial fibrillation,<br>• Gastrointestinal AEs,<br>• Potential interaction with products that can significantly affect renal function,<br>• Potential interaction with paracetamol/acetaminophen.<br>**Removal of the following missing information topics:**<br>• Use in patients with severe renal impairment.<br>**Reclassification**<br>• Atypical femur fracture (previously: important potential risk; reclassified as an important identified risk),<br>• Use in pregnancy/lactation (previously: missing information; reclassified as an important potential risk renamed "Teratogenicity") |

| Part | Major changes compared to RMP v 12.1 |
|---|---|
| | **Module SVIII** Updated to reflect the current summary of safety concerns. |
| Part III | Updated to reflect the new template requirements. Study CZOL446H2422 (category 3) is completed. It has been removed from this section. |
| Part IV | Updated to reflect the new template requirements. |
| Part V | Updated to reflect the new template requirements and the new list of safety concerns.<br>Removal of RMP educational materials assigned to the safety concerns of "Renal dysfunction" and "Use in patients with severe renal impairment" |
| Part VI | Updated to reflect the new template requirements and the new list of safety concerns. Reference to Study CZOL446H2422 was removed. |
| Part VII | Updated to reflect the new template requirements. Study CZOL446H2422 is listed as a completed study (submission date of the clinical study report was provided).<br>Removal of RMP educational materials assigned to the safety concerns of "Renal dysfunction" and "Use in patients with severe renal impairment".<br>Annex 8 was updated to reflect the summary of changes. |

## Other RMP versions under evaluation

RMP version 13.1.

**Details of the currently approved RMP:**

Version number: 12.1

Approved with procedure: EMEA/H/C/000595/II/0056

Date of approval: 25-Feb-2016 (submission date of the closing sequence)

**QPPV name:** Dr. David Lewis

**QPPV oversight declaration:** The content of this RMP has been reviewed and approved by the marketing authorization holder´s QPPV. The electronic signature is available on file.

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## List of abbreviations

| | |
|---|---|
| ADR | Adverse Drug Reaction |
| AE | Adverse Event |
| ALP | Alkaline Phosphatase |
| ALT | Alanine Aminotransferase |
| AVN | Avascular Necrosis |
| BMD | Bone Mineral Density |
| BMI | Body Mass Index |
| CHMP | Committee for medicinal products for human use |
| CI | Confidence Interval |
| COPD | Chronic obstructive pulmonary disease |
| CrCl | Creatinine Clearance |
| CSR | Clinical Study Report |
| DLP | Data lock point |
| EEA | European Economic Area |
| EMA | European Medicines Agency |
| EOP | Extended Observation Period |
| EU | European Union |
| FPPS | Farnesyl Pyrophosphate Synthase |
| GI | Gastrointestinal |
| GPRD | General Practice Research Database |
| HCP | Health Care Professional |
| LEG | Legally binding measure |
| NHANES-I | First National Health and Nutrition Examination Survey |
| oBP | Oral bisphosphonates |
| ONJ | Osteonecrosis of the Jaw |
| P3Z3 | Placebo for 3 years and zoledronic acid for the next 3 years |
| PD | Paget's Disease |
| PIP | Pediatric investigation plan |
| PRAC | Pharmacovigilance risk assessment committee |
| PRC | Patient Reminder Card |
| PSUR | Periodic Safety Update Report |
| PY | Patient Year |
| RMP | Risk Management Plan |
| RR | Reporting rate |
| SAE | Serious Adverse Event |
| SD | Standard deviation |
| SmPC | Summary of Product Characteristics |
| ZA | Zoledronic acid |
| Z3P3 | Zoledronic acid for 3 years and placebo for 3 years |
| Z6 | Zoledronic acid for 6 years |
| Z6P3 | Zoledronic acid for 6 years and placebo for 3 years |

| | |
|---|---|
| Z9 | Zoledronic acid for 9 years |

# 1 Part I: Product(s) Overview

**Table 1-1 Part I.1 - Product Overview**

| | |
|---|---|
| **Active substance (INN or common name)** | Zoledronic acid |
| **Pharmacotherapeutic group (ATC Code)** | M05BA08 |
| **Marketing Authorization Holder** | Novartis Europharm Limited |
| **Medicinal products to which this RMP refers** | 1 |
| **Invented name in the European Economic Area (EEA)** | Aclasta® |
| **Marketing authorization procedure** | Centralized. |
| **Brief description of the product** | **Chemical class:** Zoledronic acid belongs to the class of nitrogen-containing bisphosphonates. |
| | **Summary of mode of action:** Zoledronic acid acts primarily on bone. It is an inhibitor of osteoclastic bone resorption.<br>The selective action of bisphosphonates on bone is based on their high affinity for mineralized bone. The main molecular target of zoledronic acid in the osteoclast is the enzyme farnesyl pyrophosphate synthase (FPPS). The relative long duration of action of zoledronic acid is attributable to its high binding affinity for the active site of FPPS and its strong binding affinity to bone mineral. |
| | **Important information about its composition:** None. |
| **Hyperlink to the Product Information** | [Proposed SmPC] |
| **Indications in the EEA** | **Current:**<br>• Treatment of Paget's disease of the bone in adults;<br>• Treatment of osteoporosis in post-menopausal women and in adult men at increased risk of fracture, including those with a recent low-trauma hip fracture;<br>• Treatment of osteoporosis associated with long-term systemic glucocorticoid therapy in post-menopausal women and in adult men at increased risk of fracture. |
| | **Proposed:** Not applicable. |
| **Dosage in the EEA** | **Current:**<br>• **Treatment of Paget's disease**<br>Aclasta® should be prescribed only by physicians with experience in the treatment of Paget's disease of the bone. The recommended dose is a single intravenous infusion of 5 mg Aclasta®. In patients with Paget's disease, it is strongly advised that adequate supplemental calcium corresponding to at least 500 mg elemental calcium twice daily is ensured for at least 10 days following Aclasta administration.<br>Re-treatment of Paget's disease: After initial treatment with Aclasta® in Paget's disease, an extended remission period is observed in |

| | |
|---|---|
| | responding patients. Re-treatment consists of an additional intravenous infusion of 5 mg Aclasta® after an interval of one year or longer from initial treatment in patients who have relapsed. Limited data on re-treatment of Paget's disease are available.<br>Patients must be appropriately hydrated prior to administration of Aclasta®. This is especially important for the elderly and for patients receiving diuretic therapy.<br>Adequate calcium and vitamin D intake are recommended in association with Aclasta® administration.<br>• **Treatment of osteoporosis**<br>For the treatment of post-menopausal osteoporosis, osteoporosis in men and the treatment of osteoporosis associated with long-term systemic glucocorticoid therapy, the recommended dose is a single intravenous infusion of 5 mg Aclasta® administered once a year.<br>The optimal duration of bisphosphonate treatment for osteoporosis has not been established. The need for continued treatment should be re-evaluated periodically based on the benefits and potential risks of Aclasta® on an individual patient basis, particularly after 5 or more years of use.<br>In patients with a recent low-trauma hip fracture, it is recommended to give the Aclasta® infusion two or more weeks after hip fracture repair. In patients with a recent low-trauma hip fracture, a loading dose of 50 000 to 125 000 IU of vitamin D given orally or via the intramuscular route is recommended prior to the first Aclasta infusion. |
| | **Proposed:** Not applicable. |
| **Pharmaceutical form and strengths** | **Current:**<br>Intravenous use (solution for infusion).<br>Aclasta® (5 mg in 100 mL ready-to-infuse solution) is administered via a vented infusion line and given at a constant infusion rate. The infusion time must not be less than 15 minutes. |
| | **Proposed:** None. |
| **Is/will the product be subject to additional monitoring in the EU?** | No. |

# 2 Part II Safety specification Module SI: Epidemiology of the indication(s) and target population

Zoledronic acid is approved for the following indications in Europe:

- Treatment of Paget's disease of the bone in adults.
- Treatment of osteoporosis
  - in post-menopausal women,
  - in adult men at increased risk of fracture, including those with a recent low-trauma hip fracture.
- Treatment of osteoporosis associated with long-term systemic glucocorticoid therapy
  - in post-menopausal women,
  - in adult men at increased risk of fracture.

## 2.1 Indication: Paget's disease of the bone in adults

### Incidence of Paget's disease

There is little information available on the incidence of Paget's disease (PD). The true incidence is hard to determine as many people affected remain asymptomatic.

**EU countries**

Van Staa et al (2002) reported the results of a retrospective study on the incidence of PD disease in England and Wales. The data were obtained from the computerized medical records collected in General Practice Research Database (GPRD) database from 1988 to 1999.The age and sex-specific incidence rates reported (per 100000 person-years) are shown in Table 2-1.

**Non-EU countries**

A long-term study carried out in Olmsted County, Minnesota (MN), US, examined the secular trends in the incidence of the clinically diagnosed disease in a population-based survey from 1950 through 1994 (Tiegs et al 2000). A decreasing trend in global incidence rates was observed since 1980. Incidence was consistently higher in men than in women. The reported mean incidence rates for the whole period (per 100000 person-years) among white men and women are shown in Table 2-1.

**Table 2-1 Incidence of Paget's disease**

| Country/ Region Age groups (years) | Incidence rate (/100 000 PY) | | | Source of data/ reference |
|---|---|---|---|---|
| **EU countries** | **Men** | **Women** | **All (men + women)** | |
| **England and Wales/EU** | | | | |
| 50-54 | 5 | 3 | - | Van Staa et al (2002) |
| 55-59 | 12 | 8 | - | |
| 60-64 | 22 | 11 | - | |
| 65-69 | 35 | 22 | - | |

| Country/ Region<br>Age groups (years) | Incidence rate (/100 000 PY) | | | Source of data/ reference |
|---|---|---|---|---|
| 70-74 | 53 | 30 | - | |
| 75-79 | 67 | 40 | - | |
| 80-85+ | 76 | 54 | - | |
| **Total incidence** | Total incidence rate in 1997 was 6/100000 PY, decreasing from the 10/100000 PY observed in 1990 | | | |
| **Non-EU countries** | **Men** | **Women** | **All (men + women)** | |
| **Olmsted County)/USA** | | | | |
| < 35 | 0.1 | 0.1 | 0.1 | Tiegs et al 2000 |
| 35 – 39 | 0 | 0 | 0 | |
| 40 – 44 | 3.7 | 0.9 | 2.3 | |
| 45 – 49 | 2.1 | 2.0 | 2.1 | |
| 50 – 54 | 7.4 | 11.7 | 9.6 | |
| 55 – 59 | 18.6 | 15.7 | 17.1 | |
| 60 – 64 | 22.5 | 12.1 | 16.9 | |
| 65 – 69 | 47.6 | 36.2 | 41.2 | |
| 70 – 74 | 69.5 | 30.1 | 46.2 | |
| 75 – 79 | 98.5 | 29.8 | 55.7 | |
| 80 – 84 | 55.5 | 38.5 | 44.2 | |
| ≥ 85 | 121.7 | 53.1 | 71.7 | |
| **Total incidence*** | **12.7** | **7.0** | **9.2** | |
| *Age-and-gender adjusted to the US white population structure of 1990. | | | | |

## Prevalence of Paget's disease

### EU countries

The geographic variation of PD appears to be remarkable, with a high prevalence observed in Britain, but a lower prevalence in Australia, North America and parts of Western Europe. It is extremely rare in Scandinavia, Ireland and southern Europe (Cooper et al 1999, Saraux et al 2007, van Staa et al 2002).

In Europe, the results of a survey carried out in the late 1970s by means of postal questionnaires sent to radiologist practices of several countries were published (Detheridge et al 1982). The estimated prevalence of PD was found to be extremely variable among different geographic areas. In the UK, the overall frequency of PD was about 4.5%, while it was found to be 2.5% in France and ≤ 1% in southern European countries such as Spain and Italy. The prevalence in Sweden was also ≤ 1%. There were also marked differences in the prevalence figures observed in different areas of the same region.

In the UK, a radiographic survey was carried out between 1993 and 1995 in 10 towns (Cooper et al 1999). A total of 9828 radiographs from 4625 men and 5203 women aged ≥ 55 years were sampled and assessed. The overall age-and-sex-adjusted prevalence estimate of vertebral

fractures was 2.0% (95% CI: 1.8, 2.3) in men and 1.6% (95% CI: 1.3, 1.9) in women. Prevalence rates ranged from 1.2% in Carlisle up to 3.7% in Lancaster. The authors referred to a similar survey carried out in 1974 and concluded that a decreasing trend was observed among both men and women.

In a more recent study (van Staa et al 2002) a 0.3% overall prevalence of clinically diagnosed PD was estimated among those aged ≥ 55 years in the general population of England and Wales. This result contrasts with the radiographic prevalence estimates, suggesting that approximately only 7% of cases that are radiographically evident are clinically diagnosed.

In Spain, a cross-sectional study was carried out in a high frequency zone situated in the northwestern sector of the province of Salamanca (Mirón-Canelo et al 1997). The prevalence of radiologically-confirmed PD was estimated to be 5.7% (95% CI: 4.5, 6.9). Overall, 60% of the cases were diagnosed in people aged ≥ 70 years. To account for the heterogeneity in the geographical distribution of PD, the authors compared their results with previous estimates of the prevalence of PD in the whole province (1.7%) and in a northwestern sector of the bordering province of Zamora (4.8%).

The prevalence of PD in Italy was investigated from radiological, scintigraphic and biochemical surveys carried out between 1986 and 2004 in population samples from two Italian towns (Gennari et al 2005). The estimated prevalence of PD in Italy is shown in Table 2-2.

The prevalence of radiological PD ranged from 0.8% and 1.7%, while the estimated prevalence of biochemical PD was 1.5% and the scintigraphic survey showed a higher PD prevalence of 2.4%.

**Non-EU countries**

Doyle et al (2002) reported the results of a radiographic retrospective study carried out in 2001 among New Zealand "European" population (PD is considered to be extremely rare in Maori, Pacific Islanders and Asian minorities). The estimated prevalence of radiographically diagnosed PD for the New Zealand "European" population is shown in Table 2-2. Overall, the estimated prevalence of radio graphically diagnosed PD in the general population aged ≥ 55 years was 2.8% (3.6% among men, 2.0% among women), showing a substantial decline over the previous 20 years.

In the US, the First National Health and Nutrition Examination Survey (NHANES-I) obtained radiographs of the pelvic region of a representative sample of non-institutionalized civilians from the general population (4,897 men and women aged 18 - 79) between 1971 and 1975. In order to estimate the prevalence of PD, Altman et al (2000) reviewed these radiographs. The corresponding NHANES-adjusted prevalence figures are presented in Table 2-2. PD was present in 27/3423 White people and 4/475 Black people for an adjusted prevalence rate of 0.72% for Caucasians and 0.73% for Blacks. There were no cases among the 38 people who were Asian or of other origin. The ratio of men to women was 1.2:1. PD was most common in the Northeastern U.S. and least common in the South as shown in Table 2-2.

**Table 2-2 Prevalence of Paget's disease**

| Country/ Region Age groups (years) | Prevalence (%) | | | Source of data/ reference |
|---|---|---|---|---|
| | Men | Women | All (men + women) | |
| **England and Wales (general population)** | | | | van Staa et al 2002 |
| ≥ 55 | | | 0.3 | |
| **France** | | | 2.5 | |
| **Southern European countries (Italy, Spain)** | | | ≤ 1 | Detheridge et al 1982 |
| **Sweden** | | | ≤ 1 | |
| **Spain** | | | 5.7 | Mirón-Canelo et al 1997 |
| **Italy**[a] | | | | |
| ≥ 60 | 1.31 | 0.57 | 0.88 | |
| ≥ 75 | 3.58 | 1.04 | 1.75 | Gennari et al 2005 |
| **Non-EU countries** | | | | |
| **European population in New Zealand**[b] | | | | |
| 40-54 | 0.8 | 0.8 | | Doyle et al (2002) |
| 55-69 | 2.24 | 1.41 | | |
| 70-79 | 5.76 | 2.82 | | |
| ≥ 80 | 6.71 | 2.71 | | |
| **NHANES-I; 1971-1975**[b] | | | | Altman et al (2000) |
| < 35 | 0 | 0 | 0 | |
| 35 – 44 | 0.14 | 0 | 0.14 | |
| 45 – 54 | 0.37 | 0.76 | 0.48 | |
| 55 – 64 | 0.66 | 0.88 | 0.78 | |
| 65 – 74 | 3.7 | 1.3 | 2.32 | |
| 45 – 74 | 1.16 | 1.0 | 1.09 | |
| All ages | 0.59 | 0.99 | 0.71 | |
| **NHANES-I; 1971-1975; by US region** | | | | Altman et al (2000) |
| Northeast | - | - | 1.48 | |
| South | - | - | 0.26 | |
| Midwest | - | - | 0.53 | |
| West | - | - | 0.52 | |

[a]PD diagnosed by radiographic, biochemical or scientigraphic surveys; [b] PD diagnosed by radiography

In a systematic review and meta-analysis of English and non-English articles using MEDLINE (1946 to 2013) and EMBASE (1980 to 2013) carried out by Corral-Gudino et al (2013), 28 articles documented the prevalence of Paget's disease of bone (PD); 4 articles the incidence and 2 articles the rate of new referrals. The prevalence of PD varied greatly between the different countries, from 0.00028% in Japan to 5.4% in the UK. There were available data on changes in prevalence from two different surveys over two different time frames in Europe and New Zealand. In all but one city (Turin), a drop in the prevalence of PD was recorded (pooled OR 0.64; 95% CI 0.45–0.91). Overall, the review showed that the incidence and prevalence rates of PD vary widely between populations but both have decreased in most regions over recent years. The changes are heterogeneous however and within countries, the largest changes have been in areas that previously had a high prevalence. The reasons for these changes remain unclear at present but are likely to be due to an interaction between genetic factors and environmental triggers which may differ in different regions.

## Demographics of the population in the authorized indication – age, gender, racial and/or ethnic and risk factors for the disease:

**Demographic characteristics**

The demographic characteristics (age categories and gender) are presented in Table 2-1 and Table 2-2.

**Risk factors for the disease**

Factors that can increase the risk of Paget's disease of bone include:

- **Age.** People older than 40 years old are most likely to develop Paget's disease of bone;
- **Sex.** Men are slightly more commonly affected than are women;
- **National origin.** Paget's disease of bone is more common in England, Scotland, central Europe and Greece — as well as countries settled by European immigrants. It's uncommon in Scandinavia and Asia;
- **Family history:** close relatives of Paget's disease of bone.

## The main existing treatment options: Paget's disease

The main existing treatment options for PD are the following:

- Calcium: A daily intake of 800 to 1500 mg of calcium is recommended for Paget's disease patients. Supplementation is usually required;
- Vitamin D: Recommended at 800 to 1000 IU daily for persons 50 years and older. Supplementation is usually required;
- Bisphosphonates: For decreasing bone resorption through inhibition of osteoclast resorption, this drug class is the treatment of choice, as disease activity stays low for months or years after treatment;
- Calcitonin: Injectable calcitonin inhibits osteoclastic bone resorption and is also approved for treatment of Paget's disease. Compared with bisphosphonates, calcitonin is not as powerful and does not suppress the disease activity for as long after cessation.

## Natural history of the indicated condition in the population, including mortality and morbidity:

**Natural history: mortality and morbidity**

An evaluation of the natural history of PD in England and Wales, using GPRD data was conducted over an 11-year period (van Staa et al 2002, Cooper C et al 2006). The study compared 2465 patients with a recorded diagnosis of PD to 7395 controls matched by age, gender and general practice. Over the 11-year study period, patients with PD showed a greater risk of back pain (RR: 2.1; 95% CI: 1.9, 2.3), osteoarthritis (RR: 1.7; 95% CI: 1.5, 1.9) hip arthroplasty (RR: 3.1; 95% CI: 2.4, 4.1), knee arthroplasty (RR: 1.6; 95% CI: 1.0, 2.6), fracture (RR: 1.2; 95% CI: 1.0, 1.5), hip fracture (RR: 1.4; 95% CI: 1.1, 1.9) and hearing loss (RR: 1.6; 95% CI: 1.3, 1.9). A 0.1% incidence rate of malignant bone neoplasm was found among PD patients, while none of the controls developed this disease. After 5 years, 32.7% of the PD cases had died compared with 28.0% of the control group (RR: 1.3; 95% CI: 1.1, 1.4). The three most frequent causes of death during the follow-up of PD patients were diseases of the circulatory system (37.9%), neoplasms (21.8%) and diseases of the respiratory system (20.9%). These results seem to suggest that there is no evidence that PD *per se* reduces life expectancy (Altman 2002). However, PD has been shown to be associated with a significant reduction in quality of life (Saraux et al 2007).

More recent studies continue to show a decrease in the prevalence and severity of PD (Bastin et al 2009, Cundy et al 2004, Guañabens et al 2008, Poor et al 2006).

## Important co-morbidities:

The important co-morbidities associated with PD and their respective prevalence are described in Table 2-3.

**Table 2-3 Important co-morbidities associated with the Paget's disease of the bone**

| Comorbidity | Prevalence |
|---|---|
| Pathological fractures | 4.9% vs. 0.4% in matched controls 9 – 10% 19.2% |
| Spinal stenosis: cervical, thoracic, lumbar | 16.4% vs. 9.8% in matched controls |
| Low back pain | 19.7% vs. 8.6% in matched controls |
| Osteoarthritis of the hip or knee | 8.2% vs. 4.1% in matched controls; 11 – 12% |
| Joint pain | 37.3% vs. 24.6% in matched controls |
| Hearing loss | 13.5% vs. 5.7% in matched controls; 11 – 14% |
| Osteosarcoma (femur, humerus, pelvis, skull and tibia) | 0.1 - 1% |
| Heart murmur/aortic valve disease | 26% |
| Gout | 16% |
| Renal stones | 15% |
| Reduction in physical activity | 56% |

| Comorbidity | Prevalence |
|---|---|
| Source: Briesacher et al 2006, del Pino-Montes et al 2005, Gold et al 1996, Seton et al 2005, Sharma and Jane 2005. | |

## 2.2 Indication: Osteoporosis

### Incidence:

**EU countries**

In a UK-based study (GPRD database for the period 1988-98), hip fracture rate estimates were 17 for women and 5.3 for men per 10000 person-years (van Staa et al 2001).

Fracture rates increase exponentially with age in both genders and are higher in the US and Scandinavia than in Britain and Central Europe, with British population estimates being approximately 20% lower (Jordan and Cooper 2002).

An analysis of hip fracture incidence rates in 17 European countries between 1983 and 1985 showed an 11-fold range in apparent incidence amongst women and a 7-fold range amongst men between the various countries (Johnell et al 1997). The incidence was higher in women than men and there was a 3-fold range between countries in the female:male ratio. The highest incidence was found in the northern part of Europe and the lowest in the Mediterranean area. There was a significant positive correlation between age-standardized incidence rates reported in men and women from each country. In addition, there was a larger difference in incidence between countries than between genders, suggesting important genetic or environmental factors in the causation of hip fracture (Johnell et al 1997).

**Non-EU countries**

**Table 2-4 Annual age–sex-standardized hip fracture rates (per 10000 population)**

| Country/ Region | Age–sex-standardized rate | Source of data/ reference |
|---|---|---|
| Africa | From 1.17 to 5.61 | |
| Canada | From 20.54 to 27.27 | |
| China | From 6.70 to 23.58 | Cheng et al 2011 |
| Japan | From 12.09 to 17.53 | |
| USA | From 8.58 to 26.47 | |

### Prevalence:

**EU countries**

In Europe, approximately 30% of all postmenopausal women have osteoporosis and at least 40% of these women will sustain one or more fragility fractures during their remaining lifetime (Melton et al 1992). It is likely that ageing populations worldwide will be responsible for a major increase in the incidence of osteoporosis in postmenopausal women (Woolf and Pfleger 2003).

In the UK, around 23% of women aged ≥ 50 years are estimated to have osteoporosis as defined by World Health Organization (WHO). The general prevalence of osteoporosis rises exponentially from 5% among women aged 50 years to 50% at 85 years of age. Among men,

the comparable figures are 2.4% and 20%, respectively (Woolf and Pfleger 2003). The same trend has been noted in all other countries studied (Kai et al 2003, Cummings and Melton 2002, del Puente el al 1988). The highest prevalence of osteoporosis in Europe is seen in the Scandinavian countries, in particular Norway, where the incidence of hip fractures exceeds 100/10000 (Lofthus et al 2001).

**Non-EU countries**

In the US, 20% of non-Hispanic White and Asian women aged ≥ 50 years, of are estimated to have osteoporosis and 52% are estimated to have low bone mass. Furthermore, 5% of non-Hispanic Black women ≥ 50 years are estimated to have osteoporosis, with an estimated additional 35% having low bone mass, which puts them at risk of developing osteoporosis. In addition, 10% of Hispanic women aged ≥ 50 years are estimated to have osteoporosis, and 49% are estimated to have low bone mass (The National Osteoporosis Foundation 2007).

With advancing age, a greater proportion of women have a low bone mass. A population-based study in Rochester, Minnesota, US, estimated that, at the age of 80 years, 27% women are osteopenic and 70% are osteoporotic at the hip, lumbar spine or distal forearm. In the US, 54% of postmenopausal white women are osteopenic and 30% are osteoporotic. Approximately 40% of all US white women and 13% of US white men aged ≥ 50 years' experience at least one clinically apparent fragility fracture during their lifetime. In addition, 14% of women have recurrent hip fractures, while 25% of women have recurrent vertebral fractures (Jordan and Cooper 2002).

**Table 2-5 Prevalence of osteoporosis**

| Country/ Region | Prevalence | Source of data/ reference |
|---|---|---|
| **EU countries** | | |
| **Europe** | Approximately 30% of all postmenopausal women | Melton et al 1992 |
| **UK** | Around 23% of women aged ≥ 50 years<br>• 5% of women aged 50 years;<br>• 50% of women at 85 years of age. | Woolf and Pfleger 2003 |
| **Non-EU countries** | | |
| **USA** | 20% of non-Hispanic White and Asian women aged ≥ 50 years are estimated to have osteoporosis. | The National Osteoporosis Foundation 2007 |
| **USA** (population-based study in Rochester, Minnesota, US) | At the age of 80 years, 70% are osteoporotic at the hip, lumbar spine or distal forearm.<br>In the US, 30% of postmenopausal white women are osteoporotic. | Jordan and Cooper 2002 |

## Demographics of the population in the authorized indication – age, gender, racial and/or ethnic origin and risk factors for the disease:

**Demographic characteristics**

The bone mineral density (BMD) measurement is underutilized in a majority of European countries. The main reasons are as follows (International osteoporosis foundation):

- limited availability of densitometers;
- restrictions in personnel permitted to perform scans;
- low awareness of usefulness of BMD testing;
- limited or non-existent reimbursement.

Based on WHO diagnostic criteria (T-score less than or equal to -2.5 SD) approximately 22 million women and 5.5 million men aged between 50-84 years of age are estimated to have osteoporosis in the EU (International osteoporosis foundation). Due to changes in population demography the number of men and women with osteoporosis in the EU will rise from 27.5 million in 2010 to 33.9 million in 2025, corresponding to an increase of 23% (International osteoporosis foundation).

**Risk factors for the disease**

Identified significant risk factors for osteoporotic hip fractures (ordered by descending relative risk, 2 to 1.2) include the following (Lips 1997):

- Use of anticonvulsant;
- Maternal hip fracture;
- Standing < 4 hours/day;
- Inability to rise from chair;
- Previous hyperthyroidism;
- Resting pulse > 80 beats/min;
- Calcaneal bone density;
- Self-rated health (1-point decrease on a 3-point scale);
- Use of long-acting benzodiazepine;
- Any fracture since the age of 50 years;
- Aging;
- Lowest quartile for distant depth perception;
- Height at age 25 years;
- Caffeine intake (per 190 mg/day);
- Low-frequency contrast sensitivity.

## The main existing treatment options

The main existing treatment options for osteoporosis are the following:

- Calcium: A daily intake of at least 1200 mg of calcium is recommended for all women with osteoporosis. Supplementation is usually required;
- Vitamin D: Recommended at 800 to 1000 IU daily for persons 50 years and older. Supplementation is usually required;
- Bisphosphonates: Bisphosphonates inhibit osteoclastic activity and are potent antiresorptive agents. Randomized clinical trials demonstrate a reduction of fractures with different bisphosphonates;

- Raloxifene: This selective estrogen receptor modulator is approved for the treatment of post-menopausal osteoporosis. Raloxifene has estrogen agonist activity on the bones and lipids, and an estrogen antagonist effect on the breast and uterus;
- Calcitonin: Calcitonin is an anti-resorptive agent approved for the treatment of post-menopausal osteoporosis. It is not considered first-line treatment for osteoporosis because more effective medications are available;
- Teriparatide: Recombinant human parathyroid hormone with potent bone anabolic activity. In a dosage of 20 µg per day given subcutaneously for up to two years, teriparatide decreases vertebral and non-vertebral fractures;
- Denosumab: Human monoclonal antibody designed to inhibit receptor activator of nuclear factor kappa-B (RANK) ligand, a protein that acts as the primary signal for bone removal;
- Hormone therapy: Estrogen, with or without progesterone, slightly reduced the risk of hip and vertebral fractures, but this benefit must be pondered against the increased risk of vascular diseases and breast cancer, even for women at high risk of fractures.

## Natural history of the indicated condition in the untreated population, including mortality and morbidity:

**Natural history: mortality and morbidity**

Bone fractures are the major cause of morbidity and mortality associated with osteoporosis. Osteoporosis-related injuries result in complications leading to prolonged hospitalization, decreased independence, increased incidence of depression, and a reduced quality of life. In Europe, more than 37000 people die per year from fracture-related complications. Worldwide, the 5-year mortality after hip or vertebral fracture is about 20% higher than expected in the general population, with the highest mortality rate in men > 75 years suffering from a variety of chronic diseases. Most deaths occur in the first 6 months after hip fracture. One year after hip fracture, 40% of patients are still unable to walk independently, 60% have difficulty with at least one essential activity of daily living, and 80% are restricted in other activities (e.g. driving and grocery shopping). After hip fracture, 27% of patients enter a nursing home for the first time. Less is known of the epidemiology of vertebral fractures and of the associated mortality and morbidity. One reason is that two thirds of vertebral fractures remain undiagnosed. After a clinically diagnosed vertebral fracture, survival rate decreases gradually from that expected in a population without fracture (Cooper 1997).

A longitudinal study carried out between 1989 and 1994 on an Australian population aged ≥ 60 years estimated the overall incidence of bone fractures as 25.9 for women and 14.4 for men per 1000 person-years. In the general population, the mortality rates in the follow-up period were 37.2 and 49.7 per 1000 patient-years for women and men, respectively. The corresponding mortality rates in fracture patients were 73.0 (47% higher) and 166.5 (235% higher) (Center et al 1999).

More recently, a systematic review of population-based observational studies on mortality related to hip fracture after low-energy trauma showed that, compared with community controls, patients with hip fracture had an excess mortality that ranged from 8.4% to 36% during the first year after fracture. The relative risk of death after hip fracture was at least 2-fold that for age-matched control population (Abrahamsen et al 2009b). Other studies have evaluated mortality

following all types of osteoporotic fractures and showed an increased risk of death (Bliuc et al 2009, Ioannidis et al 2009, Kannegaard et al 2010).

Many risk factors for osteoporosis have been identified in cross-sectional studies. Besides low bone mineral density (BMD), age and female sex, these factors include Body Mass Index (BMI), maternal family history, prior fragility fractures, low birth weight, hormonal factors (hypogonadism, premature menopause), inadequate nutrition (low calcium and vitamin D intake), intake of medications (corticosteroid, anti-convulsant, heparin), smoking, alcohol and disease states (Cushing's disease, stroke, inflammatory arthritis) (Jordan and Cooper 2002, Lips 1997).

In the case of fractures, BMD is considered to be the single best predictor. The prediction of future fracture also depends on the presence of past fractures, with the presence of one past vertebral fracture doubling the risk of future vertebral fractures as assessed by BMD.

### Important co-morbidities:

The important co-morbidities associated with the osteoporosis/osteoporotic fractures and their respective prevalence are described in Table 2-6.

**Table 2-6 Important co-morbidities associated with the osteoporosis/osteoporotic fractures**

| Comorbidity | Prevalence |
|---|---|
| Cerebrovascular disease | 24 - 25% |
| Stroke | 9 - 13% |
| Respiratory disease/COPD | 10 - 14% |
| Renal disease | 2.5 - 3% |
| Reduced renal function | 19% |
| Diabetes | 8 - 9% |
| Rheumatoid disease | 3 - 9% |
| Parkinson's disease | 4% |
| Paget's disease | 1% |
| Current smoking | 10 - 26% |
| Use of steroids | 2% |
| No physical activity/exercise | 62 - 64% |
| Previous fractures | 41 - 55% |
| Disability/lack of mobility | 9 - 11% |
| Partial lack of mobility (rise from a chair with arms) | 49% |
| BMI < 25 kg/m$^2$ | 75.5% |
| Low body weight | 30% |

Source: Bensen et al 2005, Ensrud et al 2007, Gajic-Veljanoski et al 2007, Høidrup et al 2000, Papaioannou et al 2005, Roche et al 2005, Sennerby et al 2007.

# 3 Part II Safety specification Module SII: Non-clinical part of the safety specification

**Table 3-1 Key safety findings from non-clinical studies and relevance to human usage**

| Key Safety findings (from non-clinical studies) | Relevance to human usage |
|---|---|
| **Toxicity** | |
| **Acute or repeat-dose toxicity studies** | |
| **Renal Effects** | |
| Renal effects were observed in the animal toxicology studies, including renal tubular necrosis/regeneration and inflammation associated with elevated urea and serum creatinine. The safety margin relative to renal effects were narrow in long term parenteral studies but the cumulative no adverse event levels (NOAELs) in the multiple dose studies of up to 1 month did not indicate renal effects at doses close to or exceeding the highest recommended human therapeutic dose of Aclasta.<br>The most frequent finding in the repeat-dose studies consisted of increased primary spongiosa in the metaphyses of long bones in growing animals at nearly all doses, a finding, reflected pharmacological antiresorptive activity of zoledronic acid | Risk of renal injury in man leading to compromised renal function. Compromised renal function can be monitored in the clinic and risk management procedures are in place. |

# 4 Part II Safety specification Module SIII Clinical trial exposure

## 4.1 Part II Module SIII Clinical trial exposure

Zoledronic acid is approved for the following indications in Europe:

- Treatment of Paget's disease of the bone in adults;
- Treatment of osteoporosis
  - in post-menopausal women,
  - in adult men at increased risk of fracture, including those with a recent low-trauma hip fracture;
- Treatment of osteoporosis associated with long-term systemic glucocorticoid therapy
  - in post-menopausal women,
  - in adult men at increased risk of fracture.

Overall, the development program of zoledronic acid 5 mg in Paget's disease included 258 patients: a total of 177 patients received zoledronic acid 5 mg i.v. infusion in the combined studies and a total of 81 patients received treatment of zoledronic acid 5 mg i.v. infusion (Study CZOL446K2401).

Overall, the development program of zoledronic acid 5 mg in osteoporosis included 17026 patients in the completed controlled studies. Of these, 9319 patients received at least one dose of zoledronic acid 5 mg.

Special populations were not studied as part of the Aclasta® development program and thus exposure data are not available.

### Paget's disease

Study CZOL446K2304 and Study CZOL446K2305 were duplicate international, randomized, double-blind, double-dummy, active controlled, parallel group studies comparing the efficacy and safety over 12 months of a single i.v. zoledronic acid infusion and oral risedronate 30 mg daily for 60 days, in the treatment of patients with PD of the bone. In the combined studies, a total of 177 patients received zoledronic acid 5 mg i.v. infusion. Because multi-year remissions were anticipated to occur in response to a single 5 mg i.v. infusion, patients were to be observed periodically following the completion of the registration studies in an extended observation period (EOP) until offset of effect could be described. Follow-up data on total serum Alkaline phosphatase (ALP) levels were collected every 6 months in the EOP of the two studies. The EOP ended 15-Apr-2011.

Study CZOL446K2418 was a 6-month, open-label retreatment study of patients with PD of bone to show that patients with PD of bone, who had responded to zoledronic acid and later experienced a relapse, can successfully have their total serum ALP normalized within 6 months after a single 5 mg retreatment dose of zoledronic acid. A total of 6 patients received retreatment of zoledronic acid 5 mg i.v. infusion.

Study CZOL446K2401 was a registry study to determine incidence of hypocalcemia post Reclast® treatment in patients with Paget's disease after institution of educational strategies to improve adherence to calcium and vitamin D supplementation. A total of 81 patients received treatment of zoledronic acid 5 mg i.v. infusion.

### Osteoporosis

Patients participating in Study CZOL446H2301 meeting the entry criteria were re-randomized to a three year extension study (Study CZOL446H2301E1) to further assess long term safety and efficacy of the drug. Study CZOL446H2301E1 was an international, multicenter, randomized, double-blind 3-year extension study in postmenopausal women with osteoporosis who had completed participation in the Study CZOL446H2301 (core study). Patients who received zoledronic acid in the core study were randomized in a 1:1 fashion to receive either zoledronic acid or placebo in the extension study. Patients who received placebo in the core study were assigned to zoledronic acid in the extension study in order to retain the core study blind-status. A total of 1834 patients received zoledronic acid 5 mg as an i.v. infusion. Of these, 69 patients received 4 doses, 93 patients received 5 doses, and 451 patients received 6 doses of zoledronic acid 5 mg i.v. infusions, combined with the core Study CZOL446H2301. The population of Study CZOL446H2301 was very similar to the intended marketing population, and is considered to be predictive of the safety of zoledronic acid 5 mg in the post-marketing period.

Patients randomized to zoledronic acid treatment for up to 6 years in Study CZOL446H2301 and Study CZOL446H2301E1 have been re-randomized into a further 3-year extension study (Study CZOL446H2301E2) to continue assessing long term safety and efficacy of the drug. This study started enrolling patients in Aug-2008 and was completed on 11-Apr-2013. A total

of 190 patients were enrolled in this extension study and 92 patients received zoledronic acid 5 mg as an i.v. infusion.

Study CZOL446L2310 was a randomized, multicenter, double-blind, placebo-controlled, parallel-group study which was designed to assess the efficacy of i.v. zoledronic acid 5 mg administered annually in the prevention of subsequent clinical fractures in male and female patients following a hip fracture. The study had an endpoint-driven design, with study completion being reached when at least 211 patients had met the primary adjudicated endpoint (confirmed clinical fracture). A total of 1054 patients received zoledronic acid 5 mg as an i.v. infusion.

Study CZOL446M2308 was a randomized, multicenter, double-blind, double-dummy, active controlled, parallel-group study which was designed to determine the efficacy and safety, over 2 years, of i.v. zoledronic acid 5 mg once-yearly compared to oral alendronate 70 mg weekly for the treatment of osteoporosis in men. A total of 153 patients received zoledronic acid 5 mg as an i.v. infusion.

Study CZOL446M2309 was a 2-year multicenter, randomized, double-blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of once a year i.v. zoledronic acid 5 mg for the treatment of osteoporosis in men. A total of 1199 patients were enrolled in a 1:1 ratio to receive once a year i.v. infusion of either zoledronic acid 5 mg or placebo; 588 patients received zoledronic acid 5 mg as an i.v. infusion.

Study CZOL446N2312 was a multicenter, randomized, double-blind, placebo-controlled, parallel group study in postmenopausal women with osteopenia (low bone mass) designed to determine the efficacy and safety over 2 years of i.v. zoledronic acid 5 mg at Baseline and at 12 months, and i.v. zoledronic acid 5 mg as a single infusion at baseline only, compared to placebo. A total of 379 patients received zoledronic acid 5 mg as an i.v. infusion, 198 of whom were randomized to the once-yearly re-infusion group, and 181 were randomized to the single infusion group.

Study CZOL446O2306 was a multicenter, randomized, double-blind, double-dummy, stratified, active controlled parallel group study comparing the efficacy and safety over 12 months of a single i.v. zoledronic acid infusion and oral risedronate 5 mg daily, in the prevention and treatment of glucocorticoid-induced osteoporosis. A total of 416 patients were randomized to receive zoledronic acid 5 mg.

**Table 4-1 Exposure – number of infusions administered**

| Indication | Osteoporosis | | Osteoporosis | | Osteoporosis | | Osteoporosis | | Osteopenia | | Paget's disease | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Study number | Studies H2301/H2301E1/H2301E2 | | Study L2310 | | Studies M2308/M2309 | | Study O2306 | | Study N2312 | | Studies K2304/K2305/K2418/K2401 | |
| No. of infusions | Subject | Subject years | Subjects | Subject years | Subjects | Subject years | Subjects | Subject years | Subjects | Subject years | Subjects | Subject years |
| ≥ 1 | 5083 (100.0) | 15651.4 | 1054 (100.0) | 2057.3 | 741 (100.0) | 1412.9 | 416 (100.0) | 404.8 | 379 (100.0) | 717.2 | 258 (100.0) | 92.0 |
| 1 | 604 (11.9) | - | 314 (29.79) | - | 68 (9.2) | - | 416 (100.0) | - | 211 (10.5) | - | 252 (97.7) | - |
| 2 | 511 (10.1) | - | 416 (39.47) | - | 673 (90.8) | - | - | - | 168* (44.3) | - | 6 (3.4) | - |
| 3 | 3355 (66.0) | - | 281 (26.66) | - | - | - | - | - | - | - | - | - |
| 4 | 69 (1.4) | - | 42 (3.98) | - | - | - | - | - | - | - | - | - |
| 5 | 90 (1.8) | - | 1 (0.09) | - | - | - | - | - | - | - | - | - |
| 6 | 362 (7.1) | - | - | - | - | - | - | - | - | - | - | - |
| 7 | 13 (0.3) | - | - | - | - | - | - | - | - | - | - | - |
| 8 | 12 (0.2) | - | - | - | - | - | - | - | - | - | - | - |
| 9 | 67 (1.3) | - | - | - | - | - | - | - | - | - | - | - |

* Does not include the 2nd infusion of placebo received by ZOL 1x 5 mg group.
Source: Aclasta EU RMP version 12.1

**Table 4-2 Exposure by gender**

| Indication | Osteoporosis | | Osteoporosis | | Osteoporosis | | Osteoporosis | | Osteopenia | | Paget's disease | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Study number | Studies H2301/H2301E1/H2301E2 | | Study L2310 | | Studies M2308/M2309 | | Study O2306 | | Study N2312 | | Studies K2304/K2305/K2418/K2401 | |
| Gender | Subject | Subject years | Subjects | Subject years | Subjects | Subject years | Subjects | Subject years | Subjects | Subject years | Subjects | Subject years |
| Male | NA | NA | 244 | 459.7 | 741 | 1412.9 | 131 | 124.3 | NA | NA | 174 | 63.3 |
| Female | 5083 | 15651.4 | 810 | 1597.6 | NA | NA | 285 | 280.6 | 379 | 717.2 | 84 | 28.7 |

Source: Aclasta EU RMP version 12.1

**Table 4-3 Exposure by age group**

| Indication | Osteoporosis | | Osteoporosis | | Osteoporosis | | Osteoporosis | | Osteopenia | | Paget's disease | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Study number | Studies H2301/H2301E1/H2301E2 | | Study L2310 | | Studies M2308/M2309 | | Study O2306 | | Study N2312 | | Studies K2304/K2305/K2418/K2401 | |
| Age group | Subject | Subject years | Subjects | Subject years | Subjects | Subject years | Subjects | Subject years | Subjects | Subject years | Subjects | Subject years |
| < 65 | 7 | 20.8 | 172 | 343.6 | 330 | 635.5 | 300 | 291.3 | 277 | 519.2 | 68 | 23.8 |
| 65 – 74 | 2915 | 9367.6 | 305 | 598.5 | 285 | 538.2 | 87 | 86.8 | 84 | 164.5 | 85 | 34.1 |
| 75 – 84 | 2011 | 5886.5 | 440 | 850.7 | 122 | 231.3 | 29 | 26.7 | 18 | 33.4 | 79 | 28.5 |
| ≥ 85 | 150 | 376.5 | 137 | 264.6 | 4 | 8.0 | 0 | 0.0 | - | - | 26 | 5.6 |

Source: Aclasta EU RMP version 12.1

**Table 4-4 Exposure by dose**

| Indication | Osteoporosis | | Osteoporosis | | Osteoporosis | | Osteoporosis | | Osteopenia | | Paget's disease | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Study number | Studies H2301/H2301E1/H2301E2 | | Study L2310 | | Studies M2308/M2309 | | Study O2306 | | Study N2312 | | Studies K2304/K2305/K2418/K2401 | |
| Dose | Subject | Subject years | Subjects | Subject years | Subjects | Subject years | Subjects | Subject years | Subjects | Subject years | Subjects | Subject years |
| 5 mg | 5083 | 15651.4 | 1054 | 2057.3 | 741 | 1412.9 | 416 | 404.8 | 379 | 717.2 | 258 | 92.0 |

Source: Aclasta EU RMP version 12.1

**Table 4-5 Exposure by race**

| Indication | Osteoporosis | | Osteoporosis | | Osteoporosis | | Osteoporosis | | Osteopenia | | Paget's disease | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Study number | Studies H2301/H2301E1/H2301E2 | | Study L2310 | | Studies M2308/M2309 | | Study O2306 | | Study N2312 | | Studies K2304/K2305/K2418/K2401 | |
| Race | Subject | Subject years | Subjects | Subject years | Subjects | Subject years | Subjects | Subject years | Subjects | Subject years | Subjects | Subject years |
| Caucasian | 4078 | 12549.5 | 962 | 1876.5 | 700 | 1337.5 | 391 | 382.5 | 353 | 668.8 | 229 | 84.2 |
| Hispanic | 344 | 1102.6 | 70 | 124.9 | 0 | 0.0 | 1 | 1.0 | 14 | 26.6 | 0 | 0.0 |
| Black | 15 | 44.2 | 6 | 15.7 | 9 | 18.5 | 9 | 6.5 | 5 | 8.1 | 20 | 4.5 |
| Other | 646 | 1955.1 | 16 | 40.2 | 32 | 56.9 | 15 | 14.8 | 7 | 13.7 | 9 | 3.3 |

Source: Aclasta EU RMP version 12.1

# 5 Part II Safety specification Module SIV: Populations not studied in clinical trials

## 5.1 Part II SIV.1 Exclusion criteria in pivotal clinical studies within the development program

**Table 5-1 Important exclusion criteria in pivotal studies in the development program**

| Criteria | Reason for exclusion | Is it considered to be included as missing information? | Rationale for not including as missing information |
|---|---|---|---|
| **Hypersensitivity to the active substance, to any bisphosphonates or to any of the excipients** | Increased risk of anaphylaxis | No | The adverse drug reaction (ADR): "Hypersensitivity" is included in the label.<br>It is also mentioned as a contraindication, which means that the risk is well managed.<br>No new relevant data are expected as there is no ongoing or planned future clinical studies. |
| **Hypocalcemia** | Increased risk of hypocalcemia | No | "Hypocalcemia" is included in the label. It is also mentioned as a contraindication, which means that the risk is well managed and no new relevant data are expected as there is no ongoing or planned future clinical studies. |
| **Creatinine clearance (CrCl) < 35 mL/min** | Increased risk of renal failure | No | Lack of adequate clinical experience in this population. Renal dysfunction is well established risk and included in the label. |
| **Pregnancy and lactation** | No adequate data on use in pregnant women. Studies in animals have shown reproductive toxicological effects | Yes (regrouped under important potential risk "Teratogenicity") | Not applicable. |

## 5.2 Part II Module SIV.2. Limitations to detect adverse reactions in clinical trial development programs

Aclasta has been marketed since 02-May-2005. The cumulative exposure is approximately 7.57 million patient treatment years (PTY). Given this large clinical exposure, any limitation in ADR detection is likely to be minimal.

The extensive post-marketing exposure is also helpful to detect ADRs which could be due to prolonged exposure, cumulative effects, and which have long latency.

## 5.3 Part II Module SIV.3. Limitations in respect to populations typically underrepresented in clinical trial development programs

**Table 5-2 Exposure of special populations included or not in clinical trial development programs**

| Type of special population | Exposure |
|---|---|
| **Pregnant women** | Not included in the clinical development program. |
| **Breastfeeding women** | Not included in the clinical development program. |
| **Patients with relevant comorbidities**: | |
| • Patients with hepatic impairment | Not included in the clinical development program. |
| • Patients with renal impairment | Included in the clinical development program, but not studied in subjects with severe renal impairment (creatinine clearance < 30 ml/min), |
| • Patients with cardiovascular impairment | Not included in the clinical development program (patients with uncontrolled symptoms of cardiac failure or arrhythmia were excluded from clinical studies). |
| **Immunocompromised patients** | Not included in the clinical development program. |
| **Population with relevant different ethnic origin** | Population from different ethnic origins were included in the clinical development program (Table 4-5). |
| **Patients with a disease severity different from inclusion criteria in clinical trials** | Not Included in the clinical development program. |
| **Subpopulations carrying relevant genetic polymorphisms** | Not included in the clinical development program. |
| **Other** | |
| • Pediatric patients (< 18 years old) | Separate clinical development program conducted as PIP (34 pediatric patients were included). |
| • Elderly (≥ 65 years old) | Included in the clinical development program as part of whole population, but was not studied as a separate population (Table 4-3). |

# 6 Part II Safety specification Module SV: Post-authorization experience

## 6.1 Part II Module SV.1. Post-authorization exposure

### 6.1.1 Part II Module SV.1.1 Method used to calculate exposure

An estimate of patient exposure is calculated based on worldwide sales volume in milligrams (mg) of active substance sold during the reporting interval and the Defined Yearly Dose (DYD) of 5 mg.

The exposure is calculated in terms of PY (Patient Years) using the following formula:

$$\text{Patient exposure (PY)} = \frac{\text{Total mgs sold}}{\text{Defined yearly dose}}$$

### 6.1.2 Part II Module SV.1.2. Exposure

Aclasta has been marketed since 02-May-2005. The cumulative exposure is approximately 7.57 million patient treatment years (PTY).

**Table 6-1 Cumulative exposure from marketing experience**

| | EEA | USA and Canada | Japan | ROW |
|---|---|---|---|---|
| Aclasta 5 mg/100 mL solution (PY) | 1880400 | [redacted] | | 3534100 |

EEA: European Economic Area; ROW: Rest of the World; USA: United States of America.
This table includes cumulative data obtained: For Novartis from Apr 2005 to 31 Aug 2018, for Sandoz from Oct 2006 till 31 Aug 2018, for AKP from 25 Nov 2016 to 31 Aug 2018.
Source of data: Worldwide sales volume.

# 7 Part II Safety specification Module SVI: Additional EU requirements for the safety specification

## 7.1 Potential for misuse for illegal purposes

Abuse potential is not a known risk of bisphosphonates. While no clinical studies have been carried out to specifically investigate abuse potential, no evidence has emerged from clinical trials or from the post-marketing experience which would suggest a potential for abuse or dependence with zoledronic acid.

# 8 Part II Safety specification Module SVII: Identified and potential risks

## 8.1 Part II SVII.1. Identification of safety concerns in the initial RMP submission

### 8.1.1 Part II SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

This section is not applicable; the RMP was already approved.

### 8.1.2 SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

This section is not applicable; the RMP was already approved.

## 8.2 Part II SVII.2: New safety concerns and reclassification with a submission of an updated RMP

All the proposed changes to the list of safety concerns and missing information topics are based on GVP Module V Rev.2.

The safety concerns that were removed or reclassified since the RMP version 12.1 are described in Table 8-1.

**Table 8-1 Description of the changes done in the list of the safety concerns in comparison with RMP version 12.1**

| Safety concerns | Previous Classification | Reclassification or Removed | Rationale |
|---|---|---|---|
| **Post-dose symptoms** | Important identified risk | Removed | Post-dose symptoms are transient and reversible with decrease in incidence observed following subsequent infusions. Generally mild in nature, treated with symptomatic management. No new safety information was identified from cumulative review of all the available sources performed in the previous PSUR (DLP: 31-Aug-2018). Decrease in reporting rate (RR) and severity over last few years was observed in previous PSUR analysis (PSUR Section 16.3.1.1). Risk is well characterized and appropriately communicated through current labeling. Impact on risk-benefit balance is considered minimal. No additional PV activity ongoing. No additional risk minimization activity ongoing. No product information advising specific clinical actions. The current routine risk minimization activities are found adequate to mitigate this identified risk. In the final assessment report for the post-authorization measure LEG 037 procedure dated 30-Aug-2019 and adopted by the CHMP, the Agency agreed that no additional pharmacovigilance activities or additional risk minimization measures are necessary for this risk. However the SmPC and PIL wording should be revised to include “acute phase reactions” as separate subheading in Section 4.4 and Section 4.8. Furthermore, the Assessor suggested that `Post-dose symptoms` should be considered for removal from the safety concerns of the RMP, following the SmPC update.<br>The SmPC was updated as requested under a separate regulatory procedure (EMEA/H/C/000595/II/0074/G). A positive opinion was issued on 26-Mar-2020 together with the recommendation to remove post-dose symptoms from list of important identified risks at the next regulatory opportunity involving updates to the RMP. |
| **Renal dysfunction** | Important identified risk | Removed | Aclasta is a mature product with over 14 years of post-marketing experience. Renal dysfunction is well known risk with bisphosphonate class of drugs as they are largely eliminated by renal excretion. Risk is |

| Safety concerns | Previous Classification | Reclassification or Removed | Rationale |
|---|---|---|---|
| | | | very well characterized in label and adequately communicated with potential risk factors details and risk minimization measures. Risk minimization activities and the key message in the education material for HCP is already integrated into standard clinical practice guideline and the label. Key message in the patient educational material is communicated in the package Leaflet and also expected to be taken care by the treating physicians as Aclasta is a prescription only drug administered in the hospital set up. PSUR data over last decade indicates a downward trend in reporting of cases of renal dysfunction and the RR in last PSUR is significantly lower than the previous year (PSUR Section 16.3.1.2). There are no additional PV activities and routine risk minimization measures are deemed sufficient. The public health impact of this risk is considered low as the RR has significantly decreased over many years and routine risk minimization measures are deemed sufficient to mitigate the risk. |
| **Ocular AEs** | Important identified risk | Removed | Ocular adverse events observed with Aclasta do not threaten vision and can be managed in clinical practice by the administration of topical anti-inflammatory agents. No new safety information from all the available sources was observed in the last PSUR. Decrease in RR and severity over last few years was observed (PSUR Section 16.3.1.3). Risk is well characterized and appropriately communicated through current labeling. Impact on risk-benefit balance is considered minimal. No additional PV activity ongoing. No additional risk minimization activity ongoing. No product information advising specific clinical actions. The current routine risk minimization activities are found be adequate to mitigate this identified risk. In the PRAC assessment report for last Aclasta PSUR (EMEA/H/C/PSUSA/00009334/201808), the rapporteur agreed to remove ocular AEs from the RMP. |
| **Hypocalcemia** | Important identified risk | Removed | Well known side effect of the drug among treating physicians (bisphosphonate class effect). Well characterized and adequately communicated in label under various sections. Last 09 year PSUR data |

| Safety concerns | Previous Classification | Reclassification or Removed | Rationale |
|---|---|---|---|
| | | | does not reflect any increase in severity or specificity (PSUR Section 16.3.1.4). No additional risk minimization activity ongoing. No additional PV activities ongoing. The current routine risk minimization activities are found be adequate to mitigate this identified risk and the impact on risk-benefit balance is considered minimal. The mitigation measures outlines in the label became the standard of care in routine clinical practice. |
| **Anaphylaxis** | Important identified risk | Removed | Anaphylaxis is a risk with majority of the drugs and HCPs are clearly aware of this fact. Aclasta is administered in hospital set-up, therefore these events can be easily identified and managed well. No new safety information from all the available sources was observed in the previous PSUR. Decrease in RR and severity over last few years (PSUR Section 16.3.1.6). Risk is well characterized and appropriately communicated through current labeling and contraindication. No additional PV activity ongoing. No additional risk minimization activity ongoing. No product information advising specific clinical actions. Impact on risk-benefit balance is considered minimal. The current routine risk minimization activities are found to be adequate to mitigate this identified risk. In the PRAC assessment report for last Aclasta PSUR (EMEA/H/C/PSUSA/00009334/201808), the rapporteur agreed to remove anaphylaxis from the RMP. |
| **Osteonecrosis outside the jaw (AVN, fracture non-union and/or delayed union).** | Important potential risk | Removal | In the PRAC assessment report for last Aclasta PSUR (EMEA/H/C/PSUSA/00009334/201808) the rapporteur endorsed Novartis' proposal to remove this risk from the RMP. There are no additional risk minimization, pharmacovigilance measures or specific labelled clinical actions for this particular risk. Cumulative review in the last Aclasta PSUR (Section 16.3.2.1) did not determine a definitive causal association in patients receiving Aclasta therapy for osteoporosis indication. CDS includes a statement under Warning and Precautions: cases of osteonecrosis of other bones (including femur, hip, knee and humerus) have also been reported; however, causality has not been |

| Safety concerns | Previous Classification | Reclassification or Removed | Rationale |
|---|---|---|---|
| | | | determined in the population treated with Aclasta." In the SmPC Osteonecrosis of the external auditory canal is listed. |
| **Cerebrovascular accidents** | Important potential risk | Removed | No causal association could be established between Aclasta and CVA, over 14 years of PSUR monitoring. No new safety information from all the available sources, significant decrease in RR and no increase in severity or any serious AE related to Aclasta was observed in the last PSUR (Section 16.3.2.2).<br>Additional PV activity: Study CZOL446H2422 was completed and there was no significant difference in the risk of stroke or ischemic stroke between the zoledronic acid arm and the comparator arms and no increased risk of cardiovascular mortality. Study CZOL446H2301E1 (3-Year Extension to Study CZOL446H2301) was conducted. In Study 2301E1, the total number of stroke related AEs were 26 (4.2%) and 19 (3.1%) in the Z6 vs. Z3P3 groups respectively (p=0.29). The total number of events in the P3Z3 group was 38 (3.1%). The stroke related SAEs that occurred in the Z6 group was 3.1% compared with 1.5% in the Z3P3 group, which was not statistically significant (p=0.06). Stroke related SAEs occurred in 1.7% of P3Z3 group. In Study H2301E2, stroke SAEs occurred in 2 patients in each treatment group (Z9: cerebral infarction and ischemic stroke; Z6P3: cerebral hemorrhage and cerebrovascular accident). None of the events were considered to be related to study drug and none occurred in close proximity to study drug infusion. No product information advising specific clinical actions is needed and the current routine risk minimization activities are found to be adequate to mitigate this risk. In the PRAC assessment report for last Aclasta PSUR (EMEA/H/C/PSUSA/00009334/201808) the rapporteur endorsed Novartis' proposal to remove this risk from the RMP. |
| **Atrial fibrillation** | Important potential risk | Removed | Atrial fibrillation is already listed in the label. No new safety information from all the available sources, significant decrease in RR and no increase in severity or any serious AE related to Aclasta was observed in the last |

| Safety concerns | Previous Classification | Reclassification or Removed | Rationale |
|---|---|---|---|
| | | | PSUR (Section 16.3.2.3). The risk is appropriately communicated through current labeling.<br>Additional PV activity: Study CZOL446H2422 was completed. Novartis submitted a type II variation to the European Medicines Agency on 28-Mar-2017 (EMEA/H/C/000595/II/0069). After review of study results and further communication with EMA, Novartis concluded that the study results are consistent with the known safety profile of Aclasta in osteoporosis indication, and no new safety information were identified. PRAC and Committee for Medicinal Products for Human Use agreed with Novartis final conclusions. A summary of the safety findings of Study CZOL446H2422 is presented in Table 8-8.<br>No product information advising specific clinical actions is needed. Impact on risk-benefit balance is considered minimal. The current routine risk minimization activities are found to be adequate to mitigate this risk. In the PRAC assessment report for last Aclasta PSUR (EMEA/H/C/PSUSA/00009334/201808) the rapporteur endorsed Novartis' proposal to remove this risk from the RMP. |
| **Gastrointestinal AEs** | Important potential risk | Removed | Most common gastrointestinal (GI) AEs are non-serious and part of post-dose symptoms, and already listed in the label. No imbalance observed for the GI AEs in zoledronic acid treated patients in comparison to placebo in pooled Aclasta clinical studies. Literature review stated safe use in patients with GI problems. No new safety information from all the available sources, significant decrease in RR and no increase in severity or any serious AE related to Aclasta was observed in the PSUR (Section 16.3.2.4). Therefore GI AEs with Aclasta are identified, well characterized and appropriately communicated through current labeling. No additional PV activity ongoing. No additional risk minimization activity required. No product information advising specific clinical actions is needed. Impact on risk-benefit balance is considered minimal and the current routine risk minimization activities are found to be adequate to mitigate this risk. In the PRAC assessment report for last Aclasta PSUR |

| Safety concerns | Previous Classification | Reclassification or Removed | Rationale |
|---|---|---|---|
| | | | (EMEA/H/C/PSUSA/00009334/201808) the rapporteur endorsed Novartis' proposal to remove this risk from the RMP. |
| **Potential interaction with products that can significantly affect renal function** | Important potential risk | Removed | Renal dysfunction is well known risk with bisphosphonate class of drugs as they are largely eliminated by renal excretion. Concomitant use with another nephrotoxic drug will clearly impair and worsen renal function, so the risk is not truly considered as a potential risk. However this risk is proposed for removal from the RMP. This risk is very well characterized and adequately communicated in the label. No new safety information identified from all the available sources and cumulative no cases reported which met the severity criteria in the last PSUR (Section 16.3.2.6). Targeted follow-up checklist on renal dysfunction is sent out to ensure adequate reporting of renal related ADRs. No additional PV activity ongoing. No additional risk minimization activity needed. Impact on risk-benefit balance is considered minimal. The current routine risk minimization activities are found to be adequate to mitigate this risk. In the PRAC assessment report for last Aclasta PSUR (EMEA/H/C/PSUSA/00009334/201808) the rapporteur endorsed Novartis' proposal to remove this risk from the RMP. |
| **Potential interaction with paracetamol/acetaminophen** | Important potential risk | Removed | The studies (Study CZOL446H2315 and Study CZOL446H2407) which triggered this signal had concomitant use of high dose of paracetamol (1000 mg every 3-4 hours) which in itself is known to be associated with hepatotoxicity and most observed ALT elevations were only slightly outside the normal reference range and generally returned to normal without treatment. The CDS and SmPC in the dosage regimen mentions use of paracetamol or ibuprofen shortly following Aclasta to reduce incidence of post-dose symptoms. Cumulatively, no cases identified to substantiate this potential interaction PSUR (Section 16.3.2.7). Zoledronic acid does not inhibit human P450 enzymes. It shows no biotransformation, is excreted unchanged in urine, and protein binding is also low (around 22%). Therefore a theoretical possibility of potential interaction with paracetamol/acetaminophen that can significantly have |

| Safety concerns | Previous Classification | Reclassification or Removed | Rationale |
|---|---|---|---|
| | | | any possible hepatic impact can be ruled out. No evidence of Impact on risk-benefit balance. No additional PV activity ongoing. The available evidence thus refutes this as potential risk. In the PRAC assessment report for last Aclasta PSUR (EMEA/H/C/PSUSA/00009334/201808) the rapporteur endorsed Novartis' proposal to remove this risk from the RMP. |
| **Use in patients with severe renal impairment** | Missing information | Removed | Based on the known nephrotoxic potential of Aclasta, worsening of patient's underlying renal disease is expected to happen. Effect of Aclasta on renal functions and use in patients with severe renal impairment is well characterized and adequately communicated in label under W&P, dosage and contraindications section. No new safety information identified from all the available sources and cumulatively no cases retrieved in the last PSUR (Section 16.3.5.2) which reflects that the current routine risk minimization is working effectively. Targeted follow-up checklist on renal dysfunction is sent out to ensure adequate reporting of renal related ADRs. No additional PV activity ongoing. No additional risk minimization activity ongoing. Impact on risk-benefit balance is considered minimal. The current routine risk minimization activities are found adequate to mitigate this risk. In the PRAC assessment report for last Aclasta PSUR (EMEA/H/C/PSUSA/00009334/201808) the rapporteur endorsed Novartis' proposal to remove this missing information topic from the RMP. |
| **Atypical femur fracture** | Important potential risk | Re-classified to important identified risk | The last PSUR proposal to closely monitor this topic was endorsed by PRAC. Further PRAC stated that AFF should remain in the RMP safety specification for further characterization. There was a modest impact on individual patients and public health given the associated morbidity and chronicity of disease. The target population mainly includes elderly patients with poor bone health. The healing of fracture in this population is usually delayed and at time can be complicated with medical/surgical intervention. |

| Safety concerns | Previous Classification | Reclassification or Removed | Rationale |
|---|---|---|---|
| **Use in pregnancy/lactation** | Missing information | Re-classified to important potential risk and renamed "Teratogenicity" | Based on preclinical evidence of fetal harm, missing information "Use in pregnancy/lactation" was upgraded to potential risk in the last PSUR. Recently upgraded risks require pharmacovigilance monitoring for better characterization. If confirmed, the impact of congenital anomalies on individual patient is high. However, pregnancy is a contraindication for Aclasta therapy. In the PRAC assessment report for last Aclasta PSUR (EMEA/H/C/PSUSA/00009334/201808) the rapporteur endorsed Novartis' proposal to reclassify the risk as potential risk and rename as "Teratogenicity" in the RMP. |

# 8.3 Part II SVII.3: Details of important identified risks, important potential risks, and missing information

## 8.3.1 SVII.3.1. Presentation of important identified risks and important potential risks

### Important identified risks

#### 8.3.1.1 Important Identified Risk: Osteonecrosis of the jaw

**Table 8-2 Important Identified Risk – Osteonecrosis of the jaw**

No statistical outputs are available.

**Table 8-3 Important Identified Risk – Osteonecrosis of the jaw: Other details**

| Osteonecrosis of the jaw | Details |
|---|---|
| Potential mechanisms | Several potential mechanisms through which bisphosphonates may contribute to the development of osteonecrosis of the jaw have been raised.<br>• Preferential localization of bisphosphonate in the jaw bones compared with other skeletal sites;<br>• Greater sensitivity of jaw bone turnover to bisphosphonate inhibition compared to other skeletal sites;<br>• Accumulation of bisphosphonate in the jaw in the presence of periodontal disease, or following tooth extraction or other dental trauma, and altered bone healing response;<br>• Alteration by bisphosphonate therapy of the normal microbial flora in the oral cavity;<br>• Inhibition of the host immune response favoring mucosal or bone infection and the development of osteomyelitis;<br>• Synergistic interaction between bisphosphonate and other concomitant medications (e.g. anti-angiogenic drugs, steroids, cytotoxic chemotherapy, thalidomide, etc.).<br>However, the pathogenesis of ONJ remains unclear, and there is very limited evidence in support of the often cited, interesting but unproven hypotheses related to the pathogenesis of ONJ. |
| Evidence sources and strength of evidence | Osteonecrosis of the jaw has been reported predominantly in cancer patients treated with bisphosphonates, including zoledronic acid. Many of these patients were also receiving chemotherapy and corticosteroids. ONJ has also been reported in patients treated with oral bisphosphonates for osteoporosis or Paget's disease, but the occurrence is much rarer in these non-oncology populations.<br>Current evidence is based on the review of published literatures and post-marketing cases from safety database. ONJ is a listed event in the label. |
| Characterization of the risk | In postmenopausal women with osteoporosis, the incidence of ONJ was 0.04% at 3 years, 0.06% at 5 years and 0.44% at 10 years of treatment, suggesting that the risk of ONJ increases with duration of treatment (NOGG 2017). |

| Osteonecrosis of the jaw | Details |
|---|---|
| | In a five-year registry study Study CZOL446H2422, osteonecrosis of the jaw occurred in 12/8760 Aclasta users, 16/ 209 213 oBP users and 10/489 302 matched untreated controls. Respectively, the corresponding incidence rates were 0.5, 0.3 and 0.2 per 1 000 person years.<br>The incidence of osteonecrosis of the jaw in patients receiving bisphosphonates for benign indications is estimated to be < 1 in 100000 patient-treatment years (Khosla et al 2007). In a recent healthcare claims-based study the cumulative incidence of inflammatory conditions of the jaw, including osteonecrosis, among patients with osteoporosis who had not used bisphosphonates was 1.3 per 1000 (Cartsos et al 2008). Among 8572 survey responders of 21 years of age and older who had received oral bisphosphonates for 1 year or more the estimated incidence was 28 per 100000 person-years of oral bisphosphonate treatment (95% CI: 14, 53) (Lo et al 2010). No published data on the incidence or prevalence of osteonecrosis of the jaw in the general unexposed population are available. The published prevalence estimates for bisphosphonate users range from less than 1 per 100000 to 1 per 10000 (Khosla et al 2007, Mavrokokki et al 2007, Pazianas et al 2007). In a survey based study, the prevalence of osteonecrosis of the jaw was 0.10% (95% CI: 0.05%, 0.20%) among 8572 survey responders of 21 years of age and older who had received oral bisphosphonates for 1 year or more (Lo et al 2010).<br>Osteonecrosis of the jaw is characterized by the presence of lesions with exposed non-healing jaw bone in the oral cavity lasting more than 6 weeks after appropriate dental care. The clinical phenotype or condition currently termed as osteonecrosis of the jaw is poorly defined without stringent anatomo-pathological and clinical diagnostic criteria. Approximately 2/3 of cases affect the mandible and 1/3 the maxilla. The osteonecrosis of the jaw lesion may be painless, but the clinical presentation may also include jaw pain, toothache, altered sensation, local infection including osteomyelitis.<br>Numerous anecdotal reports and web based surveys have listed varying incidence rates for osteonecrosis of the jaw in oncology patients up to 10% (Durie et al 2005, Woo et al 2006). All these reports, however, suffer from severe methodological flaws pertaining to ascertainment bias. In the biggest retrospective cohort analysis of osteonecrosis of the jaw, which was performed at the MD Anderson Cancer Center in Houston, the overall prevalence of osteonecrosis of the jaw in patients with advanced cancer was 0.8%. According to the definition of "presence of exposed bone in the oral cavity lasting more than 3 months", 33 cases were detected in 4000 patients receiving i.v. bisphosphonates. Thirty-one cases occurred in patients with either myeloma or breast cancer yielding prevalence rates of 2.4% and 1.2% for the 2 diseases, respectively (Hoff et al 2005).<br>The incidence of osteonecrosis of the jaw in non-oncology patients treated with bisphosphonates has not been studied in prospective studies, but seems much lower than that observed in oncology patients (< 1/100000) (Nase and Suzuki 2006). |
| Risk factors and risk groups | Higher doses and more frequent use of bisphosphonate have been associated with greater ONJ risks in the oncology setting (Eastell et al 2019).<br>Risk factors for osteonecrosis of the jaw include poor oral hygiene, dental disease, dental interventions, cancer, chemotherapy or glucocorticoid therapy (Khan et al 2015). The incidence of osteonecrosis of the jaw is |

| Osteonecrosis of the jaw | Details |
|---|---|
| | substantially greater with the higher doses of bisphosphonates that are used to treat patients with skeletal metastases.<br>Multiple well documented risk factors for ONJ also include radiotherapy, and co-morbid conditions (e.g. anemia, coagulopathies and infection). |
| Preventability | Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment. A dental examination with preventive dentistry and an individual benefit-risk assessment is recommended prior to treatment with Aclasta in patients with concomitant risk factors. The following should be considered when evaluating a patient's risk of developing ONJ:<br>• Potency of the medicinal product that inhibits bone resorption (higher risk for highly potent compounds), route of administration (higher risk for parenteral administration) and cumulative dose of bone resorption therapy;<br>• Cancer, co-morbid conditions (e.g. anemia, coagulopathies, infection) and smoking;<br>• Concomitant therapies: corticosteroids, chemotherapy, angiogenesis inhibitors, radiotherapy to head and neck;<br>• Poor oral hygiene, periodontal disease, poorly fitting dentures, history of dental disease, invasive dental procedures e.g. tooth extractions.<br>All patients should be encouraged to maintain good oral hygiene, undergo routine dental check-ups, and immediately report any oral symptoms such as dental mobility, pain or swelling, non-healing of sores or discharge during treatment with zoledronic acid. While on treatment, invasive dental procedures should be performed with caution and should be avoided in close proximity to zoledronic acid treatment.<br>The management plan of the patients who develop ONJ should be set up in close collaboration between the treating physician and a dentist or oral surgeon with expertise in ONJ. Temporary interruption of zoledronic acid treatment should be considered until the condition resolves and contributing risk factors are mitigated where possible. |
| Impact on the benefit-risk balance of the product | Modest.<br>The patient's condition of underlying cancer, poor oral hygiene, dental disorders, concomitant steroids, chemotherapy and co-morbid disease is a significant risk factor for ONJ. There are risk minimization measures (Patient Reminder Card) in place to provide key precautionary messages to the patients. This risk is appropriately communicated in the label with risk minimization measures described. The review of the data received during the reporting interval did not provide any new relevant safety information pertaining to the important identified risk of ONJ. There was no increase in frequency or severity of ONJ. |
| Public health impact | Due to absence of increased risk of osteonecrosis of the jaw during the development phase and a very low RR in post-marketing setting, the potential public health impact is considered to be low. |

### 8.3.1.2 Important Identified Risk: Atypical femur fracture

**Table 8-4 Important Identified Risk – Atypical femur fracture**

No statistical outputs are available.

**Table 8-5 Important Identified Risk – Atypical femur fracture: Other details**

| Atypical femur fracture | Details |
|---|---|
| Potential mechanisms | The mechanism(s) for the development of atypical fractures in patients taking bisphosphonates is not known. However, the main postulated mechanism is the suppression of bone turnover leading indirectly to ageing bone and the delay or prevention of repair of naturally occurring stress fractures although the evidence is not conclusive. The proposed mechanisms may also apply to the development of atypical fractures in association with bisphosphonates at sites other than the femur. |
| Evidence sources and strength of evidence | Based on the data including mechanistic rationale, accumulating data from clinical studies, literatures and review of the available post-marketing data received in patients with multiple risk and confounding factors such as underlying metastatic bone lesions and/or osteoporosis, and concomitant medications (e.g. steroids and aromatase Inhibitors), the increased risk of atypical femur fractures with zoledronic acid treatment is considered well established. The risk further increases after long-term use of zoledronic acid and due to concomitant use of other osteoporotic treatments. |
| Characterization of the risk | Background incidence of atypical femoral fractures varies as definition used in different studies is not consistent. These fractures are of a distinctive radiographic appearance and can occur spontaneously or after minimal trauma. Most epidemiological studies of site-specific femur fractures have been performed using only coded discharge diagnosis.<br>In a five-year registry study Study CZOL446H2422, subtrochanteric femur or femoral shaft fractures occurred in 87/8760 Aclasta users, 166/ 209 213 oBP users and 122/489 302 matched untreated controls. Respectively, the corresponding incidence rates were 4.0, 2.6 and 1.9 per 1 000 person years.<br>Using MarketScan healthcare claims data from the period 1996-2006, Nieves et al estimated an incidence of closed subtrochanteric and shaft fractures combined of less than 25 per 100000 patient-years (Nieves et al 2010).<br>In a study using the US Nationwide Inpatient Sample, the estimated age adjusted hospitalization rates for subtrochanteric hip fractures were 34.2 (95% CI: 33.4, 34.9) and 15.4 (95% CI: 14.8, 16.0) per 100000 in women and men, respectively, in 2007 (Wang and Bhattacharyya 2011).<br>Few studies have ascertained specific radiologic features of atypical subtrochanteric fractures.<br>Huang et al (2012) evaluated the incidence of subtrochanteric fracture in a retrospective study in female members of the Kaiser Permanente Northern California aged 60 years and older with non-traumatic hip fracture during 2007-2008. The age-specific incidence rates for subtrochanteric fractures (occurring within 5 cm below (but not including) the lesser trochanter are shown below. |

| Atypical femur fracture | Details |
|---|---|
| | **Age group** / **Incidence (per 100000)**<br>60-64: 4<br>65-69: 8<br>70-74: 12<br>75-79: 19<br>80-84: 12<br>≥85: 38<br><br>In a population-based nationwide study conducted in Sweden, the radiographs of women 55 years of age or older who had a subtrochanteric or shaft fracture in 2008 were reviewed and the estimated crude incidence rate of atypical femoral fractures was 0.09 per 10000 patient-years in women non-exposed to bisphosphonates.<br><br>Literature case report series with long-term alendronate treatment (Abrahamsen et al 2009a, Goh et al 2007, Neviaser A et al 2008) have raised a question of a possibly increased risk of atypical femur fractures for other bisphosphonates. Most cases were reported with fracture sites in the "femoral shaft", "subtrochanteric femur" and "proximal femoral diaphysis" after minimal or no trauma. These fractures were considered to be "atypical" as it is uncommon for osteoporotic patients to experience a subtrochanteric fracture following a low-energy trauma (Soubrier M et al 2003). Most authors linked the presence of these fractures to low bone turnover, though the documentation of a significant low turnover state was lacking in many patients.<br>The exact frequency is unknown. Atypical fractures normally require an invasive approach with hospitalization and surgery. |
| Risk factors and risk groups | Osteoporosis is considered to be the main risk factor for fractures in the older population. Other risk factors include fluoride treatment, osteopenia, vitamin D deficiency, malnutrition, extreme exercise levels, rheumatoid arthritis, corticosteroid use, radiation therapy, renal osteodystrophy, osteomalacia, PD, hyperparathyroidism, hyperthyroidism, joint arthroplasty, diabetes mellitus and fibrous dysplasia. |
| Preventability | Bisphosphonate treatment patients should be advised to report any thigh, hip or groin pain and any patient presenting with such symptoms should be evaluated for an incomplete femur fracture. Fractures are often bilateral; therefore the contralateral femur should be examined in bisphosphonate-treated patients who have sustained a femoral shaft fracture. Discontinuation of bisphosphonate therapy in patients suspected to have an atypical femur fracture should be considered pending evaluation of the patient, based on an individual benefit risk assessment. |
| Impact on the benefit-risk balance of the product | Risk of atypical femur fracture is appropriately communicated through current labeling. No additional risk minimization measure is considered necessary. The analysis of review period data is consistent with previous cumulative analysis and did not provide any new relevant safety information pertaining to the important potential risk of atypical femur fracture. This safety concern has moderate impact on the benefit-risk balance of Aclasta. |
| Public health impact | The event appears reported in very low frequencies and the impact is deemed to be low. |

#### 8.3.1.3 Important Potential Risk: Teratogenicity

**Table 8-6 Important Potential Risk – Teratogenicity**

No statistical outputs are available.

**Table 8-7 Important Potential Risk – Teratogenicity: Other details**

| Teratogenicity | Details |
|---|---|
| Potential mechanisms | The potential risk for human is unknown.<br>In preclinical studies, teratogenicity observed in the rat study was attributed to the very potent action of the compound in lowering blood plasma calcium and binding to fetal bone. |
| Evidence sources and strength of evidence | Studies in animals with zoledronic acid have shown teratogenic effect in rats. Teratology studies were performed in two species, both via subcutaneous administration. Teratogenicity was observed in rats at doses ≥ 0.2 mg/kg and was manifested by external, visceral and skeletal malformations. No teratological or embryo/fetal effects were observed in rabbits, although maternal toxicity was marked at 0.1 mg/kg due to decreased serum calcium levels. There are no adequate and well-controlled studies of Aclasta in pregnant women. |
| Characterization of the risk | Animal reproduction studies with zoledronic acid have shown reproductive toxicity. There are no adequate data on the use of zoledronic acid in pregnant women. The potential risk for humans is unknown. Aclasta should not be used during pregnancy. Women of child-bearing potential should be advised to avoid becoming pregnant. |
| Risk factors and risk groups | Aclasta is contraindicated during pregnancy. Studies in rats have shown reproductive toxicological effects. There is a theoretical risk of fetal harm.<br>The potential risk for humans is unknown. |
| Preventability | Label recommends that Aclasta is contraindicated during pregnancy and in breast-feeding women. Women of child-bearing potential should be advised to avoid becoming pregnant while receiving Aclasta. |
| Impact on the benefit-risk balance of the product | Minimal. With current label guidance the possibility of exposure in pregnant woman is considered low. No new safety information with 18 years of post-marketing experience. |
| Public health impact | Low. The risk is appropriately communicated in the label. |

### 8.3.2 SVII.3.2. Presentation of the missing information

There is no missing information.

### 8.3.3 Study CZOL446H2422: summary of safety findings

Study CZOL446H2422 was a non-interventional post-authorization safety study using health registries to compare safety of Aclasta (zoledronic acid) against oral bisphosphonates (oBP) and untreated population controls. This study aimed at fulfilling the post-marketing commitment to the Committee for Medicinal Products for Human Use (CHMP) to perform a five-year registry study in Scandinavia, which would monitor diagnoses pertaining to cardiovascular/cerebrovascular and skeletal events in zoledronic acid-treated subjects.

The National Registries used for this study consisted of databases that routinely included all patients with prescription dispensed by pharmacies, those who were discharged from the

hospital, and those who died with a primary reason. Extracted data from these registries helped in identifying patients who were eligible to enter the study. This registry study was executed in two Scandinavian countries - Denmark and Sweden.

A total of 8760 Aclasta users (3656 from Denmark and 5104 from Sweden) were included in the study to compare with 209 213 oBP users, and further with 489 302 untreated control subjects sampled from the general population. Relevant safety findings from the study are presented in Table 8-8. Of note, there was an increased risk of heart failure, fractures, ONJ and all-cause mortality. The risk of heart failure was higher in the zoledronic acid group compared with subjects treated with oral bisphosphonates (HR 1.21; 95% CI: 1.09, 1.34). The risk was also higher when compared with matched untreated population controls (HR 1.39; 95% CI: 1.25, 1.55). The association remained significant in the adjusted analyses, but decreased (HR=1.31; 95% CI: 1.15, 1.49) when adjusted for age, previous fractures, comorbidities and previous medication. The zoledronic acid treated patients included a higher proportion of aged and frailer patients and the duration of exposure had no correlation with increase in the risk of heart failure. All-cause mortality was significantly increased in zoledronic acid users compared to the oral bisphosphonate users (HR 1.15; 95% CI: 1.07, 1.24) and untreated control subjects (HR 1.10; 95% CI: 1.02, 1.18). The risk of osteonecrosis of the jaw (ONJ) was significantly increased in the zoledronic acid users compared to the oral bisphosphonates users (HR 2.21; 95% CI: 1.03, 4.74) and to the untreated subjects (HR 3.32; 95% CI: 1.43, 7.73). Patients treated with zoledronic acid exhibited a significantly higher incidence of osteomyelitis, ONJ and fractures in general compared to matched controls. Non-hip femur fracture risk was significantly increased in the zoledronic acid users compared to the oral bisphosphonate users (HR 1.37; 95% CI: 1.09, 1.72) and untreated subjects (HR 2.05; 95% CI: 1.59, 2.63).

Taking into account the inherent limitations of epidemiological studies, the safety findings from the Study CZOL446H2422 were found to be consistent with the known safety profile of Aclasta in osteoporotic indication, and no new safety signals amongst the outcomes analyzed were identified.

**Table 8-8 Summary of safety outcomes from the 5-year registry Study CZOL446H2422 – events of interest**

| Safety outcomes of interest | Quantification of risk in comparison to untreated controls | | | | Quantification of risk in comparison to Oral Bisphosphonates (oBP) | | | |
|---|---|---|---|---|---|---|---|---|
| **Cardiovascular and cerebrovascular Safety** | | | | | | | | |
| | **Hazard Ratio (HR)** | | **95% CI** | | **Hazard Ratio (HR)** | | **95% CI** | |
| | Unadjusted | Adjusted | Unadjusted | Adjusted | Unadjusted | Adjusted | Unadjusted | Adjusted |
| Heart Failure | 1.39 | 1.31 | 1.25; 1.55 | 1.15; 1.49 | 1.21 | 1.17 | 1.09; 1.34 | 1.04; 1.32 |
| Atrial fibrillation/flutter | 1.17 | 1.18 | 1.07; 1.28 | 1.05; 1.32 | 1.02 | 0.99 | 0.93; 1.12 | 0.89; 1.11 |
| All cardiac Arrhythmias | 1.18 | 1.18 | 1.08, 1.28 | 1.06; 1.31 | 1.05 | 1.03 | 0.96; 1.14 | 0.93; 1.14 |
| Myocardial infarction (including fatal cases) | 1.13 | 1.07 | 0.94; 1.36 | 0.87; 1.33 | 0.94 | 0.90 | 0.78; 1.12 | 0.74; 1.11 |
| Stroke (hemorrhagic, ischemic) (including fatal cases) | 1.12 | 1.16 | 0.97; 1.31 | 0.98; 1.37 | 0.88 | 0.90 | 0.76; 1.01 | 0.77; 1.05 |
| Cardiovascular mortality | 0.91 | 0.87 | 0.82; 1.02 | 0.77; 0.98 | 1.01 | 1.06 | 0.90; 1.12 | 0.94; 1.19 |
| All-cause mortality | 1.10 | 1.09 | 1.02; 1.18 | 1.01; 1.18 | 1.15 | 1.24 | 1.07; 1.24 | 1.15; 1.34 |
| **Skeletal Safety** | | | | | | | | |
| | **Hazard Ratio (HR)** | | **95% CI** | | **Hazard Ratio (HR)** | | **95% CI** | |
| | Unadjusted | Adjusted | Unadjusted | Adjusted | Unadjusted | Adjusted | Unadjusted | Adjusted |
| Fracture of subtrochanteric femur or the femoral shaft | 1.94 | 2.28 | 1.45; 2.60 | 1.55; 3.35 | 1.63 | 1.91 | 1.25; 2.14 | 1.38; 2.64 |
| Osteonecrosis of the jaw (ONJ) | 3.32 | Not enough data | 1.43; 7.73 | Not enough data | 2.21 | Not enough data | 1.03; 4.74 | Not enough data |
| Osteomyelitis or necrosis, all | 2.25 | 2.27 | 1.57; 3.22 | 1.35; 3.81 | 0.98 | 0.89 | 0.72; 1.34 | 0.62; 1.28 |

| Safety outcomes of interest | Quantification of risk in comparison to untreated controls | | | | Quantification of risk in comparison to Oral Bisphosphonates (oBP) | | | |
|---|---|---|---|---|---|---|---|---|
| (Osteonecrosis outside the jaw) | | | | | | | | |
| Fractures of the appendicular skeleton | 1.47 | 1.38 | 1.33; 1.63 | 1.24; 1.54 | 0.99 | 1.02 | 0.90; 1.09 | 0.93; 1.13 |
| Fracture non-union and delayed union of fracture | 3.71 | 3.21 | 2.63; 5.21 | 1.82; 5.66 | 1.21 | 1.10 | 0.92; 1.59 | 0.79; 1.52 |
| Non-hip femur fracture | 2.05 | 2.14 | 1.59; 2.63 | 1.55; 2.95 | 1.37 | 1.57 | 1.09; 1.72 | 1.20; 2.04 |
| Source: Study CZOL446H2422 CSR, additional analysis dated 28-Sep-2017 and 27-Jul-2018, EMEA/H/C/000595/II/0069.<br>Adjusted HR - means adjusted for age, previous fractures, comorbidities and previous medication by Cox proportional hazards regression | | | | | | | | |

# 9 Part II Safety specification Module SVIII: Summary of the safety concerns

**Table 9-1 Table Part II SVIII.1: Summary of safety concerns**

| | |
|---|---|
| **Important identified risks** | Osteonecrosis of the jaw<br>Atypical femur fracture |
| **Important potential risk** | Teratogenicity |
| **Missing information** | None |

# 10 Part III: Pharmacovigilance plan (including post-authorization safety studies)

## 10.1 Part III.1. Routine pharmacovigilance activities

### 10.1.1 Routine pharmacovigilance activities beyond ADRs reporting and signal detection

**Specific adverse reaction follow-up checklists:**

Specific AE follow-up checklists will be used to collect further data to help further characterize and/or closely monitor each of the respective risks (Annex 4).

**Other forms of routine pharmacovigilance activities**

There is no other forms of routine PhV activities.

## 10.2 Part III.2. Additional pharmacovigilance activities

There are no ongoing additional pharmacovigilance activities.

## 10.3 Part III.3 Summary Table of additional pharmacovigilance activities

**Table 10-1 Part III.1: Ongoing and planned additional pharmacovigilance activities**

| Study Status | Summary of objectives | Safety concerns addressed | Milestones | Due dates |
|---|---|---|---|---|
| **Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization** | | | | |
| None. | | | | |
| **Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances** | | | | |
| None. | | | | |
| **Category 3 - Required additional pharmacovigilance activities** | | | | |

None.

# 11 Part IV: Plans for post-authorization efficacy studies

There are no efficacy studies that are specific obligations and/or conditions of the marketing authorization.

# 12 Part V: Risk minimization measures (including evaluation of the effectiveness of risk minimization activities)

## Risk Minimization Plan

## 12.1 Part V.1. Routine risk minimization measures

**Table 12-1 Table Part V.1: Description of routine risk minimization measures by safety concern**

| Safety concern | Routine risk minimization activities |
|---|---|
| **Important identified risks** | |
| **Osteonecrosis of the jaw** | **Routine risk communication**<br>SmPC Section 4.4., Section 4.8, and Package leaflet (PL) Section 2.<br>**Routine risk minimization activities recommending specific clinical measures to address the risk**<br>Risk factors, preventive measures of ONJ are included in SmPC Section 4.4 and Section 4.8.<br>Symptoms of ONJ, potential risk factors and preventive measures are mentioned in PL Section 2 and Section 4.<br>**Other routine risk minimization measures beyond the Product Information:**<br>None. |
| **Atypical femur fracture** | **Routine risk communication**<br>SmPC Section 4.4, Section 4.8, and PL Section 2.<br>**Routine risk minimization activities recommending specific clinical measures to address the risk**<br>Clinical picture, imaging feature for diagnosis and the statement that AFF is reported primarily in patients receiving long-term treatment for osteoporosis is mentioned in SmPC Section 4.4.<br>Atypical femoral fracture is mentioned as a possible side effect with Aclasta and also includes details on symptoms of disease in PL Section 4.<br>**Other routine risk minimization measures beyond the Product Information:**<br>None. |
| **Important potential risks** | |
| **Teratogenicity** | **Routine risk communication**<br>SmPC Section 4.3, Section 4.6, and Package leaflet Section 2.<br>**Routine risk minimization activities recommending specific clinical measures to address the risk** |

| Safety concern | Routine risk minimization activities |
|---|---|
| | Contraindication of Aclasta use in pregnant women is included in SmPC Section 4.4 and Section 4.6. Aclasta is not recommended in women of childbearing potential is mentioned in Section 4.6.<br>Advice that Aclasta should not be taken if patient is pregnant, think she may be pregnant or are planning to have a baby is in mentioned in PL Section 2.<br>**Other routine risk minimization measures beyond the Product Information:**<br>None. |
| **Missing information** | |
| None | |

## 12.2 Part V.2. Additional Risk minimization measures

### Patient alert card

For the important identified risk of osteonecrosis of the jaw, the routine risk minimization activities are supplemented with an additional risk minimization measure: a patient reminder card (PRC) is part of the patient information pack.

**Objectives:**

To minimize the risk of ONJ as much as possible, by further extending the awareness to the patient.

**Rationale for the additional risk minimization activity:**

Since Aclasta is being administered once a year, the patient should have adequate information available, so that they can prevent the occurrence of ONJ by taking appropriate measures/precautions.

**Target audience and planned distribution path:**

Patient reminder cards will be distributed locally to physicians for dissemination to patients receiving Aclasta.

**Plans to evaluate the effectiveness of the interventions and criteria for success:**

The effectiveness of the patient reminder card in the EU for the risk of osteonecrosis of the jaw was evaluated by monitoring the number and the RR of the relevant cases of osteonecrosis of jaw in a separate LEG. In addition, post marketing RR of the relevant cases of ONJ in the EU before and after the introduction of the patient card with its comparison to the respective data of rest of the world were also monitored and presented in a separate report (assessment report for the post-authorization measure LEG 035; submitted on 27-Oct-2016).

Furthermore, as a process indicator Novartis will continue to monitor the extent of delivery of the PRC through existing Novartis tools, processes at the global and local levels, and present this in future PSURs.

## 12.3 Part V.3 Summary of risk minimization measures

**Table 12-2 Summary of pharmacovigilance activities and risk minimization activities by safety concerns**

| Safety concern | Risk minimization measures | Pharmacovigilance activities |
|---|---|---|
| **Important identified risks** | | |
| **Osteonecrosis of the jaw** | **Routine risk minimization measures**<br>SmPC Section 4.4 and Section 4.8.<br>Package leaflet Section 2: What you need to know before you are given Aclasta.<br>**Additional risk minimization measures**.<br>Novartis introduced and implemented PRC for the patients receiving Aclasta. | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**:<br>Targeted follow-up checklist.<br>**Additional pharmacovigilance activities**:<br>None. |
| **Atypical femur fracture** | **Routine risk minimization measures**<br>SmPC Section 4.4 and Section 4.8.<br>Package leaflet Section 2: What you need to know before you are given Aclasta.<br>**Additional risk minimization measures**.<br>None. | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**:<br>Targeted follow-up checklist.<br>**Additional pharmacovigilance activities**:<br>None. |
| **Important potential risks** | | |
| Teratogenicity | **Routine risk minimization measures**<br>SmPC Section 4.3 and Section 4.6.<br>Package leaflet Section 2: What you need to know before you are given Aclasta.<br>**Additional risk minimization measures**.<br>None. | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**:<br>None<br>**Additional pharmacovigilance activities**:<br>None. |
| **Missing information** | | |
| None | | |

# 13 Part VI: Summary of the risk management plan for Aclasta (zoledronic acid)

This is a summary of the risk management plan (RMP) for Aclasta. The RMP details important risks of Aclasta, how these risks can be minimized, and how more information will be obtained about Aclasta's risks and uncertainties (missing information).

Aclasta's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Aclasta should be used.

This summary of the RMP for Aclasta should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Aclasta's RMP.

## 13.1 Part VI: I. The medicine and what it is used for

Aclasta is authorized for:

- Treatment of Paget's disease of the bone in adults;
- Treatment of osteoporosis in post-menopausal women and in adult men at increased risk of fracture, including those with a recent low-trauma hip fracture;
- Treatment of osteoporosis associated with long-term systemic glucocorticoid therapy in post-menopausal women and in adult men at increased risk of fracture.

Aclasta contains zoledronic acid (powder and solvent for solution for infusion) as the active substance.

Further information about the evaluation of Aclasta's benefits can be found in Aclasta's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage:

https://www.ema.europa.eu/en/documents/overview/aclasta-epar-summary-public_en.pdf

## 13.2 Part VI: II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of Aclasta, together with measures to minimize such risks and the proposed studies for learning more about Aclasta's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In the case of Aclasta, these measures are supplemented with additional risk minimization measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

### 13.2.1 Part VI – II.A: List of important risks and missing information

Important risks of Aclasta are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Aclasta. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

**Table 13-1 List of important risks and missing information**

| List of important risks and missing information | |
|---|---|
| **Important identified risks** | Osteonecrosis of the jaw<br>Atypical femur fracture |
| **Important potential risks** | Teratogenicity |
| **Missing information** | None |

### 13.2.2 Part VI - II B: Summary of important risks

## Important identified risks

**Table 13-2 Important identified risk – Osteonecrosis of the jaw**

| | |
|---|---|
| **Evidence for linking the risk to the medicine** | Osteonecrosis of the jaw has been reported predominantly in cancer patients treated with bisphosphonates, including zoledronic acid. Many of these patients were also receiving chemotherapy and corticosteroids. ONJ has also been reported in patients treated with oral bisphosphonates for osteoporosis or Paget's disease, but the occurrence is much rarer in these non-oncology populations.<br>Current evidence is based on the review of published literatures and post-marketing cases from safety database. ONJ is a listed event in the label. |
| **Risk factors and risk groups** | Higher doses and more frequent use of bisphosphonate have been associated with greater ONJ risks in the oncology setting.<br>Osteonecrosis of the jaw has multiple well documented risk factors including a diagnosis of cancer, concomitant therapies (e.g. chemotherapy, radiotherapy, corticosteroids) and co-morbid conditions (e.g. anemia, coagulopathies, infection, pre-existing dental disease). |
| **Risk minimization measures** | **Routine risk minimization measures**<br>SmPC Section 4.4 and Section 4.8.<br>**Additional risk minimization measures**<br>Novartis introduced and implemented patient alert card for the patients receiving Aclasta. |

**Table 13-3 Important identified risk – Atypical femur fracture**

| | |
|---|---|
| **Evidence for linking the risk to the medicine** | Based on the data including mechanistic rationale, accumulating data from clinical studies, literatures and review of the available post-marketing data received in patients with multiple risk and |

| | |
|---|---|
| | confounding factors such as underlying metastatic bone lesions and/or osteoporosis, and concomitant medications (e.g. steroids and aromatase Inhibitors), the increased risk of atypical femur fractures with zoledronic acid treatment is considered well established. This risk further increases after long-term use of zoledronic acid and due to concomitant use of other osteoporotic treatments. |
| **Risk factors and risk groups** | Osteoporosis is considered to be the main risk factor for fractures in the older population. Other risk factors include fluoride treatment, osteopenia, vitamin D deficiency, malnutrition, extreme exercise levels, rheumatoid arthritis, corticosteroid use, radiation therapy, renal osteodystrophy, osteomalacia, PD, hyperparathyroidism, hyperthyroidism, joint arthroplasty, diabetes mellitus and fibrous dysplasia. |
| **Risk minimization measures** | **Routine risk minimization measures**<br>SmPC Section 4.4 and Section 4.8.<br>**Additional risk minimization measures**<br>None. |

## Important Potential Risks

**Table 13-4 Important identified risk – Teratogenicity**

| | |
|---|---|
| **Evidence for linking the risk to the medicine** | Studies in animals with zoledronic acid have shown reproductive toxicological effects including malformations. Teratology studies were performed in two species, both via subcutaneous administration. Teratogenicity was observed in rats at doses ≥ 0.2 mg/kg and was manifested by external, visceral and skeletal malformations. No teratological or embryo/fetal effects were observed in rabbits, although maternal toxicity was marked at 0.1 mg/kg due to decreased serum calcium levels. There are no adequate and well-controlled studies of Aclasta in pregnant women. |
| **Risk factors and risk groups** | Aclasta is contraindicated during pregnancy. Studies in rats have shown reproductive toxicological effects. There is a theoretical risk of fetal harm.<br>The potential risk for humans is unknown. |
| **Risk minimization measures** | **Routine risk minimization measures**<br>SmPC Section 4.3 and Section 4.6.<br>**Additional risk minimization measures**<br>None. |

### 13.2.3 Part VI – II C: Post-authorization development plan

#### 13.2.3.1 II.C.1 Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorization or specific obligation of Aclasta.

#### 13.2.3.2 II.C.2. Other studies in post-authorization development plan

There are no studies required for Aclasta.

# 14 Part VII: Annexes

## Table of contents

## Annex 4 - Specific adverse drug reaction follow-up forms

This annex contains the specific adverse event targeted follow-up checklists used to collect additional data for the following Aclasta RMP risks:

- Osteonecrosis of the jaw;
- Atypical Femoral Fractures.

# Bisphosphonate Osteonecrosis of the Jaw

**Name of checklist (version/date)**: Bisphosphonate osteonecrosis of the jaw (ONJ) (version 6.0/Apr 2018).

**Targeted Follow-up Checklist**
**Bisphosphonate**
**Osteonecrosis of the Jaw (ONJ)**

ONJ is exposed bone in the oral cavity with no evidence of healing after 6 weeks of appropriate evaluation and dental care in the absence of metastatic disease in the jaw or osteoradionecrosis.

In addition to collecting routine information for this adverse event, please ensure the following additional information is provided and/or confirmed.

**Has the patient previously received the Patient Reminder Card (PRC) on ONJ:** ☐ Yes ☐ No ☐ Don't know
**(This question is applicable for Aclasta & Zometa and EU/EEA countries ONLY)**

**Did the patient have a dental examination with preventive dentistry prior to treatment with Aclasta/Zometa (Zoledronic acid)?**
☐ Yes ☐ No ☐ Don't know

**Information on Dose of suspected medication:**

| Drug name | Dose | Dosing regimen | Treatment date |
|---|---|---|---|
| | | | |
| | | | |
| | | | |

**Information on event duration:**

| Event | Diagnosis date | Dental treatment date | Event end date |
|---|---|---|---|
| ONJ | | | |
| | | | |
| | | | |

**Event Description:**

Did the patient present with any of the following signs or symptoms? ***Check all that apply***

☐ Area surrounding lesion red and/or swollen
☐ Spontaneous pain
☐ Pain on palpation
☐ Suppuration (pus)
☐ Swollen/tender lymph nodes on same side as lesion
☐ Unable to eat
☐ None of the above

Where was the jaw location of the observed lesion? *(Please include the overall size)*

☐ Upper left ☐ Lower left
☐ Upper front ☐ Lower front
☐ Upper right ☐ Lower right

| Length (cm) | Width (cm) |
|---|---|
| | |

Is bone exposed? ☐ **Yes** *(please specify the largest dimension below)* ☐ **No** ☐ **Unknown**
**If Yes,** largest dimension is: ☐ <0.5 cm ☐ 0.5-0.99 cm ☐ 1.0-1.99 cm ☐>1.99 cm

*NOTE: If bone is exposed, please contact the treating dentist / oral surgeon / periodontist to submit copies of the X-ray films/reports and dental notes describing the initial, follow-up and final presentations.*

Is the event accompanied by a bone/soft tissue infection?
☐ **Yes** *(please specify including method of diagnosis (e.g. biopsy with isolated pathogen(s)))* ☐ **No** ☐ **Unknown**

Has the patient experienced complications of the reported event(s) (e.g. pathological fracture, fistula)?
☐ **Yes** *(please specify)* ☐ **No** ☐ **Unknown**

Was treatment given for the condition/symptoms?
☐ **Yes** *(please specify)* ☐ **No** ☐ **Unknown**

---

**Relevant medical history (concurrent and pre-existing conditions)**
***(Please specify medical condition and date of onset)***

Does the patient have a history of any of the following risk factors? ***Check all that apply and specify including dates***

☐ Cancer
☐ Chemotherapy
☐ Radiotherapy to head and neck area
☐ Treatment with corticosteroids
☐ Poor oral hygiene
☐ Dental/oral problems (e.g. periodontal/ dental infections, toothache, stomatitis, oral ulcers)
☐ Dental treatments (e.g. fillings, crowns, root canal treatments, routine cleanings, deep scaling, orthodontics)
☐ Dental-surgical procedures (e.g. routine/surgical tooth extractions, periodontal surgery, implants)
☐ Impaired healing after dental procedure
☐ Trauma or fractures upper/lower jaw
☐ None of the above

**Previous use of bisphosphonates or other antiresorptive agents:**

Has the patient taken any of the following drugs? ***Check all that apply and detail below***
☐ bisphosphonates ☐ other antiresorptive agents ☐ other

List details for the above drugs as appropriate:

| Drug | Route of administration | Dosing regimen or daily dose | Dates of treatment (dd/mm/yyyy) | Indication for use |
|---|---|---|---|---|

| | | | Start date | Stop date | |
|---|---|---|---|---|---|
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |

## Bisphosphonate Atypical Femoral Fractures

**Name of checklist (version/date):** Bisphosphonate atypical femoral fractures (version 3.0/May 2018).

**Targeted Follow-Up Checklist**
**Bisphosphonates**
**Atypical Femoral Fractures**

This targeted follow-up checklist aims to collect major and minor features of atypical femoral fractures, as defined by the Task Force of the American Society of Bone and Mineral Research (Shane E et al., JBMR, 2014). In addition to collecting routine information for this adverse event, please ensure the following additional information is provided and/or confirmed.

Is the femoral fracture located along the femoral diaphysis from just distal to the lesser trochanter to just proximal to the supracondylar flare?

☐ Yes ☐ No, the fracture is either above or below these limits ☐ Unknown

**Major Features:**

**1)** Was the fracture associated with no or minimal trauma (such as fall from standing height or less)?

☐ Yes ☐ No, the fracture was associated with a significant trauma ☐ Unknown

**2)** Does the fracture line originates at the lateral cortex and have a transverse or short-oblique configuration?

☐ Yes ☐ No, the fracture does not have transverse or short-oblique configuration (e.g. spiral fracture) ☐ Unknown

**3)** Is the fracture non-comminuted or minimally comminuted?

☐ Yes ☐ No, the fracture is comminuted ☐ Unknown

**4)** The fracture is: **a)** ☐ complete **b)** ☐ incomplete ☐ Unknown

**4a)** If the fracture is complete:

Does the fracture extend through both cortices?

☐ Yes ☐ No ☐ Unknown

Is the fracture associated with a medial spike?

☐ Yes ☐ No ☐ Unknown

**4b)** If the fracture is incomplete:

Does the fracture involve the lateral cortex?

☐ Yes ☐ No, the fracture involves only the medial cortex ☐ Unknown

**5)** Are there localized periosteal or endosteal thickening of the lateral cortex is present at the fracture site (e.g. breaking or flaring)

☐ Yes ☐ No ☐ Unknown

**Supporting Information:**

Please provide copies of all relevant source documents. (E.g., radiograph assessments, bone density results, operative notes, and pathology reports [e.g., histomorphometric analyses of iliac crest bone biopsies]).

**Minor Features**

| | |
|---|---|
| **1)** Is there a generalized increase in the cortical thickness of the femoral diaphysis? | ☐ Yes ☐ No ☐ Unknown |
| **2)** Were there unilateral or bilateral prodromal symptoms, such as dull or aching pain in the groin or thigh? | ☐ Yes ☐ No ☐ Unknown |
| **3)** Were there bilateral incomplete or complete femoral diaphysis fractures? | ☐ Yes ☐ No ☐ Unknown |
| **4)** Was there a delayed healing of the fracture? | ☐ Yes ☐ No ☐ Unknown |

**5)** Were there relevant co-morbid conditions?

| | | | |
|---|---|---|---|
| a) Vitamin D deficiency | ☐ Yes | ☐ No | ☐ Unknown |
| b) Rheumatoid arthritis | ☐ Yes | ☐ No | ☐ Unknown |
| c) Hypophosphatasia | ☐ Yes | ☐ No | ☐ Unknown |
| d) Other (please specify): | | | |

**6)** Did the patient take any of the following medications? **Check all that apply:**

☐ Glucocorticoids
☐ Proton pump inhibitors

# Annex 6 - Details of proposed additional risk minimization activities (if applicable)

## Patient reminder card:

**This reminder card contains important safety information that you need to be aware of before and during treatment with Aclasta (zoledronic acid).**

Your doctor has recommended that you receive Aclasta (zoledronic acid), which is used to treat post-menopausal women and adult men with osteoporosis or osteoporosis caused by treatment with steroids, and Paget's disease of the bone in adults. These diseases involve thinning and weakening of the bones so they may break more easily.

A side effect called osteonecrosis of the jaw (ONJ) (severe bone damage in the jaw) has been reported very rarely in patients receiving zoledronic acid for osteoporosis. ONJ can also occur after stopping treatment.

It is important to try and prevent the development of ONJ as it is a painful condition that can be difficult to treat. In order to reduce the risk of developing ONJ, there are some precautions you should take:

**Before starting treatment:**

Tell your doctor/nurse (health care professional) if you have any problems with your mouth or teeth.

Your doctor may ask you to undergo a dental examination if you:

- were previously treated with another bisphosphonate medication
- are taking medicines called corticosteroids (such as prednisolone or dexamethasone)
- are a smoker
- have cancer
- have not had a dental check up for a long time
- have problems with your mouth or teeth

**While being treated:**

- You should maintain good oral hygiene, brush your teeth regularly and receive routine dental check-ups. If you wear dentures you should make sure these fit properly.
- If you are under dental treatment or will undergo dental surgery (e.g. tooth extractions), inform your doctor and tell your dentist that you are being treated with zoledronic acid
- Contact your doctor and dentist immediately if you experience any problems with your mouth or teeth such as loose teeth, pain or swelling, or non-healing of sores or discharge, as these could be signs of osteonecrosis of the jaw