16 February 2012
EMA/225612/2012
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Zoledronic acid Actavis

International non-proprietary name: zoledronic acid

Procedure No. EMEA/H/C/002488

Assessment Report as adopted by the CHMP with
all information of a commercially confidential nature deleted.

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1. Background information on the procedure

1.1. Submission of the dossier

The applicant Actavis Group PTC ehf submitted on 10 May 2011 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Zoledronic acid Actavis, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004– 'Generic of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 20 January 2011.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product for which a Marketing Authorisation is or has been granted in the Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication:
Prevention of skeletal related events (pathological fractures, spinal compression, radiation or surgery to bone, or tumour-induced hypercalcaemia) in patients with advanced malignancies involving bone.
Treatment of tumour-induced hypercalcaemia (TIH).

The legal basis for this application refers to:

Generic application (Article 10(1) of Directive No 2001/83/EC).

The application submitted is composed of administrative information and complete quality data. There is no requirement for bioequivalence testing according to (cf.CPMP/QWP/EWP/1401/98 Rev. 1).

Information on paediatric requirements

Not applicable.

The chosen reference product is:

- Medicinal product which is or has been authorised in accordance with Community provisions in accordance with Community provisions in force for not less than 6/10 years in the EEA:
  - Product name, strength, pharmaceutical form: Zometa, 4mg/5ml, powder and solvent for solution for infusion and ZOMETA 4 mg/ 5ml concentrate for solution for infusion
  - Marketing authorisation holder: Novartis Europharm Ltd.
  - Date of authorisation: 20/03/2001
  - Marketing authorisation granted by: Community
    - Community Marketing authorisation number: EU/1/01/176/001- 006

- Medicinal product authorised in the Community where the application is made or European reference medicinal product:
  - Product name, strength, pharmaceutical form: Zometa 4 mg/ 5ml concentrate for solution for infusion
  - Marketing authorisation holder: Novartis Europharm Ltd. - UK
  - Marketing authorisation granted by: Community
    - Community Marketing authorisation number: EU/1/01/176/004 - 006

Scientific advice

The applicant did not seek scientific advice at the CHMP.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP and the evaluation team were:

Rapporteur: Dr. Milena Stain

- The application was received by the EMA on 10 May 2011.
- The procedure started on 25 May 2011.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 12 August 2011.
- During the meeting on 19 – 22 September 2011 the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 23 September 2011.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 17 October 2011
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 25 November 2011.
- During the CHMP meeting on 12 – 15 December the CHMP agreed on a list of outstanding issues to be sent to the applicant. The final consolidated List of Outstanding Issues was sent to the applicant on 16 December 2011.
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 22 December 2011
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 10 February 2012.
- During the meeting on 16 February 2012, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Zoledronic acid Actavis 4mg/5ml concentrate for solution for infusion on 16 February 2012.

2. Scientific discussion

2.1. Introduction

Zoledronic acid is a bisphosphonate. It stops the action of the osteoclasts, the cells in the body that are involved in breaking down the bone tissue. This leads to less bone loss. The reduction of bone loss helps to make bones less likely to break, which is useful in preventing fractures in cancer patients with bone metastases.

Patients with tumours can have high levels of calcium in their blood, released from the bones. By preventing the breakdown of bones, Zoledronic acid also helps to reduce the amount of calcium released into the blood.

Zoledronic acid Actavis 4mg/5ml concentrate for solution for infusion is a generic application made according to Article 10(1) of Directive 2001/83/EC. For this application, the reference medicinal product authorised in the Community not less than 6/10 years ago is Zometa 4 mg powder and solvent for solution for infusion, by Novartis Europharm Limited, registered since 20.March 2001 in the EU (centrally authorised, EU/1/01/176/001-003).

The Applicant claims essential similarity for their product Zoledronic acid Actavis 4 mg/5 ml concentrate for solution for infusion with the reference product Zometa 4 mg/5 ml concentrate for solution for infusion, authorised as a line extension to Zometa 4 mg powder and solvent for solution for infusion on 24 March 2003 (EU/1/01/176/004-006) and this license belongs to the same global marketing authorization.

Since at the time of administration to the patient, the solutions are aqueous in nature, contain the same active substance in equal amounts, and given that they are intended for parenteral administration, there is no requirement for bioequivalence testing (cf.CPMP/QWP/EWP/1401/98 Rev. 1).

The applicant applied for all the indications of the reference product (Zometa) :

- Prevention of skeletal related events (pathological fractures, spinal compression, radiation or surgery to bone, or tumour-induced hypercalcaemia) in adult patients with advanced malignancies involving bone.

- Treatment of adult patients with tumour-induced hypercalcaemia (TIH).

Zoledronic acid Actavis must only be prescribed and administered to patients by healthcare professionals experienced in the administration of intravenous bisphosphonates.

The recommended dose in the prevention of skeletal related events in patients with advanced malignancies involving bone is 4 mg zoledronic acid every 3 to 4 weeks ; patients should also be administered an oral calcium supplement of 500 mg and 400 IU vitamin D daily. The decision to treat patients with bone metastases for the prevention of skeletal related events should consider that the onset of treatment effect is 2-3 months.

The recommended dose in hypercalcaemia is a single dose of 4 mg zoledronic acid.

In patients with renal impairment, the dosing instructions and monitoring of serum creatinine as detailed in SmPC section 4.2 should be followed.

Zoledronic acid Actavis 4 mg/5 ml concentrate for solution for infusion, further diluted in 100 ml should be given as a single intravenous infusion in no less than 15 minutes. Patients must be maintained well hydrated prior to and following administration of Zoledronic acid Actavis.

The safety and efficacy of zoledronic acid in children aged 1 year to 17 years have not been established.

2.2. Quality aspects

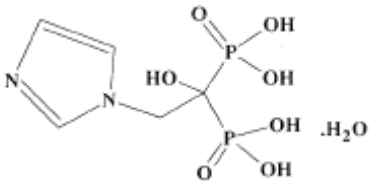
2.2.1. Introduction

Zoledronic Acid Actavis 4 mg/5 ml concentrate for solution for infusion is intended for intravenous infusion. The drug product solution is further diluted in 0.9% sodium chloride injection or 5% w/v glucose solution prior to administration. The drug product solution looks like a clear, colourless solution.

The product is contained in 5 ml sterile plastic vials, which meet the requirements of the Ph. Eur., and are closed with type I bromobutyl rubber stoppers and sealed with aluminium seals with polypropylene caps.

2.2.2. Active substance

This medicinal product contains Zoledronic acid (INN), as monohydrate. This is a white or practically white, odourless crystalline powder, sparingly soluble in 0.1N Sodium hydroxide solution and slightly soluble in water.



Chemical Name: [1-Hydroxy-2-(1H-imidazol-1-yl)ethylidene]- bisphosphonic acid or 2-(Imidazol-1-yl)-1- hydroxyethane-1,1-diphosphonic acid

This molecule is optically inactive, *and polymorphic* form has been investigated with X-ray diffraction and was concluded to be Form I.

Manufacture

At the time of the CHMP opinion, the active substance is supplied by two active substance manufacturers. Detailed information about the manufacturing process, control of starting materials, reagents and solvents, control of critical steps and intermediates, process development and process validation of the active substance has been supplied in the form of active substance master files (ASMF). All manufacturing steps are adequately described. Adequate in process controls are in place and appropriate specifications have been adopted for the starting materials, solvents and reagents. All relevant impurities, degradation products and residual solvents have been appropriately characterized.

Specification

Zoledronic acid monohydrate is not subject of an official pharmacopoeia. In-house specifications were established by both manufacturers covering all relevant tests such as appearance, solubility (Ph.Eur), identification (IR, HPLC), pH (Ph.Eur), Water (KF), Phosphites (HPLC), heavy metals, related substances (HPLC), assay (HPLC), residual solvents (GC).

The specifications are adequate to control the quality of the active substance. The impurity limits are acceptable and there is no concern from the point of view of safety.

Stability

Stability studies were performed in accordance with current ICH/CHMP guidelines and are still ongoing. Test methods applied for stability tests are the same as methods for routine testing.

One of the manufactures submitted results of three production batches for a time period of 48 months long term stability data, and studies performed at 40°C±2°C/75%±5%RH for three production batches for a time period of 6 months. The obtained results for the parameters tested were within specified limits.

The second manufacturer submitted data from the stability study of batches stored for 6 months (40±2°C/75±5% RH) and for 36/60 months (25±2°C/60±5% RH). Forced degradation studies were also conducted. The obtained results for the parameters tested were within specified limits.

Based on the stability data presented by both manufacturers, the corresponding retest periods have been accepted.

2.2.3. Finished medicinal product

Pharmaceutical development

The product Zoledronic Acid 4 mg/5 ml concentrate for solution for infusion has been formulated according to the scope it was intended for, i.e., respectively, its route of administration (intravenous infusion) and its pharmaceutical form (concentrate for solution for infusion), based on the available data in the literature and using the innovator product Zometa® as reference.

The applied sterilization method, terminal steam autoclave, demonstrated to be the most suitable for the finished product and it guaranteed the quality of the finished product with respect to the Quality Specification at release; this cycle, 25 minutes at 121.5°C, was successfully validated.

The formulation contains the same excipients used in the reference product. All of them are well known and widely used in the pharmaceutical industry. Each excipient is described in the European Pharmacopoeia

Adventitious agents

The Drug Product Zoledronic Acid 4 mg/5 ml concentrate for solution for infusion does not contain any materials of animal and/or human origin which could represent a potential risk concerning TSE/ BSE contamination.

Manufacture of the product

The manufacturing process of Zoledronic acid 4 mg/ 5 ml concentrate for solution for infusion is a standard process for parenteral formulations. The manufacturing process consists of four main steps: dissolution, filtration, filling and terminal moist heat sterilisation. The required manufacturing parameters and ranges were determined during manufacturing process development and process validation.

Preliminary process validation study on three pilot batches of Zoledronic Acid 4 mg/5 ml (about 87% of the amount of the proposed industrial batch size) were performed with the aim of evaluating the active substance behaviour, the chemical and microbiological stability of the finished product and checking the reproducibility and robustness of the manufacturing process and its critical steps. A formal process validation study will be performed on three consecutive full-scale (or commercial) batches following the scheme proposed in the validation protocol and the results of the study will be available before the product is placed on the market.

Product specification

The release and shelf life specification of Zoledronic acid Actavis includes tests and limits for appearance of solution (Visual, Ph.Eur), pH value (Potentiometric, Ph.Eur), extractable volume (Ph.Eur), Identification (HPLC and colorimetric), Subvisible particles(Ph.Eur), Assay and related substances (HPLC), Bacterial endotoxins (Ph.Eur), Sterility (Ph.Eur), water loss (only shelf life)

Specifications for the finished product at release and during shelf life are adequate for quality control. All methods were described sufficiently.

Results of batch analyses were presented. All the presented results were within the specification limits and confirm both the consistency of production and good performance of the analysis methods. It can be concluded that the analytical tests are suitable, manufacturing process and analysis are well controlled.

Stability of the product

Stability data under long-term, intermediate and accelerated conditions were provided.

Three pilot batches of Zoledronic Acid 4 mg/5 ml concentrate for solution for infusion were manufactured and introduced in stability program for the testing periods and conditions: 6 months under accelerated conditions (40°C ± 2°C/75% RH ± 5°C), 36 months on long term conditions (25°C ± 2°C/60% RH ± 5°C) and 36 months on intermediate conditions (30°C ± 2°C/75% RH ± 5°C). Furthermore stability data for photo stability, stability data of the drug product after dilution, stability data of the drug product after freeze-thaw cycles and stability study of drug product which underwent a second terminal sterilization cycle (doubled sterilized vials) were submitted

For the parameters Appearance, Colour, Clarity, pH, Visible particles, Sub-visible particles, bacterial endotoxin and sterility no significant changes were noticed for the available period of study, as compared to the initial testing point, and there are no differences regardless of the storage conditions.

The stability results of the samples stored at accelerated and long-term conditions for Zoledronic acid 4mg/5ml concentrate for solution for infusion are well within all parameters of the drug product specification.

Based on available stability data, the proposed shelf life and storage conditions as stated in the SmPC are acceptable.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendation(s) for future quality development

Not applicable.

2.3. Non- clinical aspects

2.3.1. Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

Therefore, the CHMP agreed that no further non-clinical studies are required.

2.3.2. Pharmacology

No Environmental Risk Assessment was submitted. This was justified by the applicant as the introduction of Zoledronic acid Actavis from Actavis Group PTC ehf is considered unlikely to result in any significant increase in the combined sales volumes for all zoledronic acid containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar and not increased.

2.3.3. Pharmacokinetics

Not applicable

2.3.4. Toxicology

Not applicable

2.4. Clinical aspects

2.4.1. Introduction

This is an application for Concentrate for solution for infusion containing 4 mg/5 ml zoledronic acid.

The Applicant claims essential similarity for their product Zoledronic acid Actavis 4 mg/5 ml concentrate for solution for infusion with the reference product Zometa 4 mg/5 ml concentrate for solution for infusion.

GCP

Not applicable

Exemption

There are no bioequivalence studies submitted with this application. Bioequivalence testing with the reference product is not required under the provisions of the "Guideline on the Investigation of Bioequivalence" (CPMP/QWP/EWP/1401/98 Rev.1):

"Bioequivalence studies are generally not required if the test product is to be administered as an aqueous intravenous solution containing the same active substance as the currently approved product".

The pharmaceutical form and mode of administration as well as the qualitative and quantitative composition of Zoledronic acid Actavis 4 mg/5 ml concentrate for solution for infusion is the same as of the reference product Zometa 4 mg/5 ml concentrate for solution for infusion.

The claim of essential similarity can be accepted. There are no objections to the approval of Zoledronic acid Actavis 4 mg/5 ml concentrate for solution for infusion from a clinical point of view.

Clinical studies

2.4.2. Pharmacokinetics

Not applicable

2.4.3. Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

2.4.4. Discussion on clinical aspects

Not applicable

2.4.5. Conclusions on clinical aspects

A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. The clinical aspects of the SmPC are in line with the SmPC of the reference product.

Therefore, the CHMP agreed that no further clinical studies are required.

2.5. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk management plan

The applicant submitted a risk management plan.

Table 1. Summary of the risk management plan.

<table>
<tr><th>Safety issue</th><th>Agreed pharmacovigilance activities</th><th>Agreed risk minimisation activities</th></tr>
<tr><td colspan="3">Important identified risks</td></tr>
<tr><td>Renal function impairment</td><td>Routine pharmacovigilace including cumulative analysis in PSUR.

Additional activities: Extended follow up of spontaneous, literature and Actavis Clinical trial case reports using a checklist.</td><td>Information is included in labelling (SPC sections 4.2, 4.4, 4.5, and 4.8)

Section 4.2: Posology and method of administration
Renal impairment
TIH:
Zoledronic acid Actavis treatment in TIH patients who also have severe renal impairment should be considered only after evaluating the risks and benefits of treatment. In the clinical studies, patients with serum creatinine > 400 micromol/l or > 4.5 mg/dl were excluded. No dose adjustment is necessary in TIH patients with serum creatinine < 400 micromol/l or < 4.5 mg/dl (see section 4.4).

Prevention of skeletal related events in patients with advanced malignancies involving bone:
When initiating treatment with Zoledronic acid Actavis in patients with multiple myeloma or metastatic bone lesions from solid tumours, serum creatinine and creatinine clearance (CLcr) should be determined. CLcr is calculated from serum creatinine using the Cockcroft-Gault formula. Zoledronic acid Actavis is not recommended for patients presenting with severe renal impairment prior to initiation of therapy, which is defined for this population as CLcr < 30 ml/min. In clinical trials with zoledronic acid, patients with serum creatinine > 265 micromol/l or > 3.0 mg/dl were excluded.

In patients with bone metastases presenting with mild to moderate renal impairment prior to initiation of therapy, which is defined for this population as CLcr 30-60 ml/min, the following Zoledronic acid Actavis dose is recommended (see also section 4.4):
<table><tr><th>Baseline Creatinine Clearance (ml/min)</th><th>Zoledronic acid Actavis recommended dose</th></tr><tr><td>> 60</td><td>4.0 mg zoledronic acid</td></tr></table></td></tr>
</table>

Safety issue	Agreed pharmacovigilance activities	Agreed risk minimisation activities

50-60	3.5 mg* zoledronic acid
40-49	3.3 mg* zoledronic acid
30-39	3.0 mg* zoledronic acid

* Doses have been calculated assuming target AUC of 0.66 (mg•hr/l) (CLcr = 75 ml/min). The reduced doses for patients with renal impairment are expected to achieve the same AUC as that seen in patients with creatinine clearance of 75 ml/min.

Following initiation of therapy, serum creatinine should be measured prior to each dose of Zoledronic acid Actavis and treatment should be withheld if renal function has deteriorated. In the clinical trials, renal deterioration was defined as follows:

- For patients with normal baseline serum creatinine (< 1.4 mg/dl or < 124 micromol/l), an increase of 0.5 mg/dl or 44 micromol/l;
- For patients with abnormal baseline creatinine (> 1.4 mg/dl or > 124 micromol/l), an increase of 1.0 mg/dl or 88 micromol/l.

In the clinical studies, zoledronic acid treatment was resumed only when the creatinine level returned to within 10% of the baseline value (see section 4.4). Zoledronic acid Actavis treatment should be resumed at the same dose as that given prior to treatment interruption.
[...]

Method of administration
[...]
In patients with mild to moderate renal impairment, reduced zoledronic acid doses are recommended (see section "Posology" above and section 4.4).

Instructions for preparing reduced doses of Zoledronic acid Actavis
Withdraw an appropriate volume of the concentrate needed, as follows:

- 4.4 ml for 3.5 mg dose
- 4.1 ml for 3.3 mg dose
- 3.8 ml for 3.0 mg dose

Safety issue	Agreed pharmacovigilance activities	Agreed risk minimisation activities
		The withdrawn amount of concentrate must be further diluted in 100 ml of sterile 0.9% w/v sodium chloride solution or 5% w/v glucose solution. The dose must be given as a single intravenous infusion over no less than 15 minutes. [...] Section 4.4 Special warnings and precautions for use [...] Renal insufficiency Patients with TIH and evidence of deterioration in renal function should be appropriately evaluated with consideration given as to whether the potential benefit of treatment with Zoledronic acid Actavis outweighs the possible risk. The decision to treat patients with bone metastases for the prevention of skeletal related events should consider that the onset of treatment effect is 2-3 months. Zoledronic acid, used as indicated in sections 4.1 and 4.2, has been associated with reports of renal dysfunction. Factors that may increase the potential for deterioration in renal function include dehydration, pre-existing renal impairment, multiple cycles of zoledronic acid and other bisphosphonates as well as use of other nephrotoxic medicinal products. While the risk is reduced with a dose of 4 mg zoledronic acid administered over 15 minutes, deterioration in renal function may still occur. Renal deterioration, progression to renal failure and dialysis have been reported in patients after the initial dose or a single dose of 4 mg zoledronic acid. Increases in serum creatinine also occur in some patients with chronic administration of zoledronic acid at recommended doses for prevention of skeletal related events, although less frequently. Patients should have their serum creatinine levels assessed prior to each dose of Zoledronic acid Actavis. Upon initiation of treatment in patients with bone metastases with mild to moderate renal impairment, lower doses of zoledronic acid are recommended. In patients who show evidence of renal deterioration during treatment, Zoledronic acid Actavis should be withheld.

Safety issue	Agreed pharmacovigilance activities	Agreed risk minimisation activities
		Zoledronic acid Actavis should only be resumed when serum creatinine returns to within 10% of baseline. Zoledronic acid Actavis treatment should be resumed at the same dose as that given prior to treatment interruption. In view of the potential impact of zoledronic acid on renal function, the lack of clinical safety data in patients with severe renal impairment (in clinical trials defined as serum creatinine ≥ 400 micromol/l or ≥ 4.5 mg/dl for patients with TIH and ≥ 265 micromol/l or ≥ 3.0 mg/dl for patients with cancer and bone metastases, respectively) at baseline and only limited pharmacokinetic data in patients with severe renal impairment at baseline (creatinine clearance < 30 ml/min), the use of Zoledronic acid Actavis is not recommended in patients with severe renal impairment. [...] Section 4.5 Interaction with other medicinal products and other forms of interaction [...] Caution is indicated when Zoledronic acid Actavis is used with other potentially nephrotoxic medicinal products. Attention should also be paid to the possibility of hypomagnesaemia developing during treatment. In multiple myeloma patients, the risk of renal dysfunction may be increased when Zoledronic acid Actavis is used in combination with thalidomide. Section 4.8 Undesirable effects [...] The following are the important identified risks with zoledronic acid in the approved indications: Renal function impairment, osteonecrosis of the jaw, acute phase reaction, hypocalcaemia, ocular adverse events, atrial fibrillation, anaphylaxis. The frequencies for each of these identified risks are shown in Table 1. Tabulated list of adverse reactions The following adverse reactions, listed in Table 1, have been accumulated from clinical studies and post-marketing reports following predominantly chronic treatment with 4 mg zoledronic acid:

Safety issue	Agreed pharmacovigilance activities	Agreed risk minimisation activities
		Table 1 [...] Renal and urinary disorders Common: Renal impairment Uncommon: Acute renal failure, haematuria, proteinuria [...] Description of selected adverse reactions: Renal function impairment Zoledronic acid, used as indicated in sections 4.1 and 4.2, has been associated with reports of renal dysfunction. Factors that may increase the potential for deterioration in renal function include dehydration, pre-existing renal impairment, multiple cycles of zoledronic acid or other bisphosphonates, as well as concomitant use of nephrotoxic medicinal products or using a shorter infusion time than currently recommended. Renal deterioration, progression to renal failure and dialysis have been reported in patients after the initial dose or a single dose of 4 mg zoledronic acid (see section 4.4). [...]
Osteonecrosis of the jaw	Routine pharmacovigilace including cumulative analysis in PSUR. Additional activities: Extended follow up of spontaneous, literature and Actavis Clinical trial case reports using a checklist.	Information is included in labelling (SPC sections 4.4, and 4.8) Section 4.4 Special warnings and precautions for use [...] Osteonecrosis of the jaw Osteonecrosis of the jaw has been reported in patients, predominantly those with cancer, receiving treatment with medicinal products that inhibit bone resorption, such as zoledronic acid. Many of these patients were also receiving chemotherapy and corticosteroids. The majority of reported cases have been associated with dental procedures such as tooth extraction. Many had signs of local infection including osteomyelitis. A dental examination with appropriate preventive dentistry should be considered prior to treatment with bisphosphonates in patients with concomitant risk factors (e.g. cancer, chemotherapy, corticosteroids, poor oral hygiene).

Safety issue	Agreed pharmacovigilance activities	Agreed risk minimisation activities
		While on treatment, these patients should avoid invasive dental procedures if possible. For patients who develop osteonecrosis of the jaw while on bisphosphonate therapy, dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of osteonecrosis of the jaw. Clinical judgement of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment. [...] Section 4.8 Undesirable effects [...] The following are the important identified risks with zoledronic acid in the approved indications: Renal function impairment, osteonecrosis of the jaw, acute phase reaction, hypocalcaemia, ocular adverse events, atrial fibrillation, anaphylaxis. The frequencies for each of these identified risks are shown in Table 1. Tabulated list of adverse reactions The following adverse reactions, listed in Table 1, have been accumulated from clinical studies and post-marketing reports following predominantly chronic treatment with 4 mg zoledronic acid: Table 1 [...] Musculoskeletal and connective tissue disorders Common: Bone pain, myalgia, arthralgia, generalised pain Uncommon: Muscle cramps, osteonecrosis of the jaw* [...] *Based on clinical trials with adjudication of possible cases of osteonecrosis of the jaw. Since these reports are subject to confounding factors, it is not possible to reliably establish a causal relationship to exposure to the medicinal product [...]

Safety issue	Agreed pharmacovigilance activities	Agreed risk minimisation activities
		Osteonecrosis of the jaw Cases of osteonecrosis (primarily of the jaws) have been reported, predominantly in cancer patients treated with medicinal products that inhibit bone resorption, such as zoledronic acid. Many of these patients had signs of local infection including osteomyelitis, and the majority of the reports refer to cancer patients following tooth extractions or other dental surgeries. Osteonecrosis of the jaws has multiple documented risk factors including a diagnosis of cancer, concomitant therapies (e.g. chemotherapy, radiotherapy, corticosteroids) and co-morbid conditions (e.g. anaemia, coagulopathies, infection, pre-existing oral disease). Although causality has not been determined, it is recommended to avoid dental surgery as recovery may be prolonged (see section 4.4). [...]
Acute phase reaction	Routine pharmacovigilace including cumulative analysis in PSUR.	Information is included in labelling (SPC sections 4.8) Section 4.8 Undesirable effects Summary of the safety profile Within three days after zoledronic acid administration, used as indicated in sections 4.1 and 4.2, an acute phase reaction has commonly been reported, with symptoms including bone pain, fever, fatigue, arthralgia, myalgia and rigors; these symptoms usually resolve within a few days (see description of selected adverse reactions). The following are the important identified risks with zoledronic acid in the approved indications: Renal function impairment, osteonecrosis of the jaw, acute phase reaction, hypocalcaemia, ocular adverse events, atrial fibrillation, anaphylaxis. The frequencies for each of these identified risks are shown in Table 1. [...] Acute phase reaction This adverse drug reaction consists of a constellation of symptoms that includes fever, myalgia, headache, extremity pain, nausea, vomiting, diarrhoea and arthralgia. The onset time is ≤ 3 days post-zoledronic acid infusion (used as indicated in sections 4.1 and 4.2), and the reaction is also referred to using the terms "flu-

Safety issue	Agreed pharmacovigilance activities	Agreed risk minimisation activities
		like" or "post-dose" symptoms. [...]
Hypocalcemia	Routine pharmacovigilace including cumulative analysis in PSUR.	Information is included in labelling (SPC sections 4.2, 4.4, and 4.8) Section 4.2 Posology and method of administration [...] Patients should also be administered an oral calcium supplement of 500 mg and 400 IU vitamin D daily. [...] Section 4.4 Special warnings and precautions for use [...] Standard hypercalcaemia-related metabolic parameters, such as serum levels of calcium, phosphate and magnesium, should be carefully monitored after initiating Zoledronic acid Actavis therapy. If hypocalcaemia, hypophosphataemia, or hypomagnesaemia occurs, short-term supplemental therapy may be necessary. Untreated hypercalcaemia patients generally have some degree of renal function impairment, therefore careful renal function monitoring should be considered. [...] Section 4.8 Undesirable effects [...] The following are the important identified risks with zoledronic acid in the approved indications: Renal function impairment, osteonecrosis of the jaw, acute phase reaction, hypocalcaemia, ocular adverse events, atrial fibrillation, anaphylaxis. The frequencies for each of these identified risks are shown in Table 1. Tabulated list of adverse reactions The following adverse reactions, listed in Table 1, have been accumulated from clinical studies and post-marketing reports following predominantly chronic treatment with 4 mg zoledronic acid: Table 1 Investigations Very common: Hypophosphataemia

Safety issue	Agreed pharmacovigilance activities	Agreed risk minimisation activities
		Common: Blood creatinine and blood urea increased, hypocalcaemia Uncommon: Hypomagnesaemia, hypokalaemia Rare: Hyperkalaemia, hypernatraemia [...]
Ocular adverse events	Routine pharmacovigilace including cumulative analysis in PSUR. Additional activities: Extended follow up of spontaneous, literature and Actavis Clinical trial case reports using a checklist	Information is included in labelling (SPC section 4.8) Section 4.8 Undesirable effects [...] The following are the important identified risks with zoledronic acid in the approved indications: Renal function impairment, osteonecrosis of the jaw, acute phase reaction, hypocalcaemia, ocular adverse events, atrial fibrillation, anaphylaxis. The frequencies for each of these identified risks are shown in Table 1. Tabulated list of adverse reactions The following adverse reactions, listed in Table 1, have been accumulated from clinical studies and post-marketing reports following predominantly chronic treatment with 4 mg zoledronic acid: Table 1 [...] Eye disorders Common: Conjunctivitis Uncommon: Blurred vision, scleritis and orbital inflammation Very rare: Uveitis, episcleritis [...]
Atrial fibrillation	Routine pharmacovigilace including cumulative analysis in PSUR. Additional activities: Extended follow up of	Information is included in labelling (SPC section 4.8) Section 4.8 Undesirable effects [...] The following are the important identified risks with zoledronic acid in the approved indications:

Safety issue	Agreed pharmacovigilance activities	Agreed risk minimisation activities
	spontaneous, literature and Actavis Clinical trial case reports using a checklist	Renal function impairment, osteonecrosis of the jaw, acute phase reaction, hypocalcaemia, ocular adverse events, atrial fibrillation, anaphylaxis. The frequencies for each of these identified risks are shown in Table 1. Tabulated list of adverse reactions The following adverse reactions, listed in Table 1, have been accumulated from clinical studies and post-marketing reports following predominantly chronic treatment with 4 mg zoledronic acid: Table 1 [...] Cardiac disorders Uncommon: Hypertension, hypotension, atrial fibrillation, hypotension leading to syncope or circulatory collapse Rare: Bradycardia [...] Atrial fibrillation In one 3-year, randomised, double-blind controlled trial that evaluated the efficacy and safety of zoledronic acid 5 mg once yearly vs. placebo in the treatment of postmenopausal osteoporosis (PMO), the overall incidence of atrial fibrillation was 2.5% (96 out of 3,862) and 1.9% (75 out of 3,852) in patients receiving zoledronic acid 5 mg and placebo, respectively. The rate of atrial fibrillation serious adverse events was 1.3% (51 out of 3,862) and 0.6% (22 out of 3,852) in patients receiving zoledronic acid 5 mg and placebo, respectively. The imbalance observed in this trial has not been observed in other trials with zoledronic acid, including those with zoledronic acid 4 mg every 3-4 weeks in oncology patients. The mechanism behind the increased incidence of atrial fibrillation in this single clinical trial is unknown. [...]
Anaphylaxis	Routine pharmacovigilace including cumulative analysis in PSUR	Information is included in labelling (SPC section 4.8) Section 4.8 Undesirable effects [...]

Safety issue	Agreed pharmacovigilance activities	Agreed risk minimisation activities
		The following are the important identified risks with zoledronic acid in the approved indications: Renal function impairment, osteonecrosis of the jaw, acute phase reaction, hypocalcaemia, ocular adverse events, atrial fibrillation, anaphylaxis. The frequencies for each of these identified risks are shown in Table 1. Tabulated list of adverse reactions The following adverse reactions, listed in Table 1, have been accumulated from clinical studies and post-marketing reports following predominantly chronic treatment with 4 mg zoledronic acid: Table 1 [...] Immune system disorders Uncommon: Hypersensitivity reaction Rare: Angioneurotic oedema [...]
Important potential risks		
Atypical femoral fracture	Routine pharmacovigilace including cumulative analysis in PSUR and close monitoring. Additional activities: Extended follow up of spontaneous, literature and Actavis Clinical trial case reports using a checklist	Atypical femoral fracture is included in labelling (SPC section 4.4 and 4.8) Section 4.4 Special warnings and precautions for use [...] Atypical fractures of the femur Atypical subtrochanteric and diaphyseal femoral fractures have been reported with bisphosphonate therapy, primarily in patients receiving long-term treatment for osteoporosis. These transverse or short oblique fractures can occur anywhere along the femur from just below the lesser trochanter to just above the supracondylar flare. These fractures occur after minimal or no trauma and some patients experience thigh or groin pain, often associated with imaging features of stress fractures, weeks to months before presenting with a completed femoral fracture. Fractures are often bilateral; therefore the contralateral femur should be examined in bisphosphonate-treated patients who have sustained a femoral shaft fracture. Poor healing of these

Safety issue	Agreed pharmacovigilance activities	Agreed risk minimisation activities
		fractures has also been reported. 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. During 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. Section 4.8 Undesirable effects [...] Atypical fractures of the femur During post-marketing experience the following reactions have been reported (frequency rare): Atypical subtrochanteric and diaphyseal femoral fractures (bisphopsphonate class adverse reaction).
Cardiac arrhythmias	Routine pharmacovigilace including cumulative analysis in PSUR. Additional activities: Extended follow up of spontaneous, literature and Actavis Clinical trial case reports using a checklist	Atrial fibrillation and bradycardia are included in labelling (SPC section 4.8) Section 4.8 Undesirable effects [...] Cardiac disorders Uncommon: Hypertension, hypotension, atrial fibrillation, hypotension leading to syncope or circulatory collapse Rare: Bradycardia [...]
Cerebrovascular AEs	Routine pharmacovigilace including cumulative analysis in PSUR. Additional activities: Extended follow up of spontaneous, literature and Actavis Clinical trial case reports using a checklist	Currently available data do not support the need for risk minimization

Safety issue	Agreed pharmacovigilance activities	Agreed risk minimisation activities
Focal segmental Glomerulosclerosis	Routine pharmacovigilace including cumulative analysis in PSUR.	Currently available data do not support the need for risk minimization
Fracture healing impariment	Routine pharmacovigilace including cumulative analysis in PSUR.	Currently available data do not support the need for risk minimization
Interstitial lung disease	Routine pharmacovigilace including cumulative analysis in PSUR.	Currently available data do not support the need for risk minimization
Potential interactions		
Products that can significantly affect renal function	Routine pharmacovigilance	Information is included in labelling (SPC sections 4.4 and 4.5) Section 4.4 Special warnings and precautions for use [...] Zoledronic acid, used as indicated in sections 4.1 and 4.2, has been associated with reports of renal dysfunction. Factors that may increase the potential for deterioration in renal function include dehydration, pre-existing renal impairment, multiple cycles of zoledronic acid and other bisphosphonates as well as use of other nephrotoxic medicinal products. While the risk is reduced with a dose of 4 mg zoledronic acid administered over 15 minutes, deterioration in renal function may still occur. Renal deterioration, progression to renal failure and dialysis have been reported in patients after the initial dose or a single dose of 4 mg zoledronic acid. Increases in serum creatinine also occur in some patients with chronic administration of zoledronic acid at recommended doses for prevention of skeletal related events, although less frequently. [...] Section 4.5 Interaction with other medicinal products and other forms of interaction [...] Caution is indicated when Zoledronic acid Actavis is used with other potentially nephrotoxic medicinal products. Attention should also be paid to the possibility of

Safety issue	Agreed pharmacovigilance activities	Agreed risk minimisation activities
		hypomagnesaemia developing during treatment. In multiple myeloma patients, the risk of renal dysfunction may be increased when Zoledronic acid Actavis is used in combination with thalidomide.
Important missing information		
Races other than Caucasian	Routine pharmacovigilance	Currently available data do not support the need for risk minimization.
Fertility, Pregnancy and Lactation	Routine pharmacovigilance	Information is included in labelling (SPC sections 4.3 and 4.6) Section 4.3 Contraindications [...] • Breast-feeding (see section 4.6) [...] Section 4.6 Fertility, pregnancy and lactation Pregnancy There are no adequate data on the use of zoledronic acid in pregnant women. Animal reproduction studies with zoledronic acid have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Zoledronic acid Actavis should not be used during pregnancy. Breast-feeding It is not known whether zoledronic acid is excreted into human milk. Zoledronic acid Actavis is contraindicated in breast-feeding women (see section 4.3). Fertility Zoledronic acid was evaluated in rats for potential adverse effects on fertility of the parental and F1 generation. This resulted in exaggerated pharmacological effects considered to be related to the compound's inhibition of skeletal calcium metabolisation, resulting in periparturient hypocalcaemia, a bisphosphonate class effect, dystocia and early termination of the study. Thus these results precluded determining a definitive effect of zoledronic acid on fertility in humans.
Patient with severe renal impairment	Routine pharmacovigilance	Information is included in labelling (SPC sections 4.2, 4.4, 4.5 and 4.8)

Safety issue	Agreed pharmacovigilance activities	Agreed risk minimisation activities
		Section 4.2 Posology and method of administration [...] Renal impairment TIH: Zoledronic acid Actavis treatment in TIH patients who also have severe renal impairment should be considered only after evaluating the risks and benefits of treatment. In the clinical studies, patients with serum creatinine > 400 micromol/l or > 4.5 mg/dl were excluded. No dose adjustment is necessary in TIH patients with serum creatinine < 400 micromol/l or < 4.5 mg/dl (see section 4.4). Prevention of skeletal related events in patients with advanced malignancies involving bone: When initiating treatment with Zoledronic acid Actavis in patients with multiple myeloma or metastatic bone lesions from solid tumours, serum creatinine and creatinine clearance (CLcr) should be determined. CLcr is calculated from serum creatinine using the Cockcroft-Gault formula. Zoledronic acid Actavis is not recommended for patients presenting with severe renal impairment prior to initiation of therapy, which is defined for this population as CLcr < 30 ml/min. In clinical trials with zoledronic acid, patients with serum creatinine > 265 micromol/l or > 3.0 mg/dl were excluded. In patients with bone metastases presenting with mild to moderate renal impairment prior to initiation of therapy, which is defined for this population as CLcr 30-60 ml/min, the following Zoledronic acid Actavis dose is recommended (see also section 4.4): Baseline Creatinine Clearance (ml/min) — Zoledronic acid Actavis recommended dose > 60 — 4.0 mg zoledronic acid 50-60 — 3.5 mg* zoledronic acid 40-49 — 3.3 mg* zoledronic acid 30-39 — 3.0 mg* zoledronic acid

Safety issue	Agreed pharmacovigilance activities	Agreed risk minimisation activities
		* Doses have been calculated assuming target AUC of 0.66 (mg•hr/l) (CLcr = 75 ml/min). The reduced doses for patients with renal impairment are expected to achieve the same AUC as that seen in patients with creatinine clearance of 75 ml/min. Following initiation of therapy, serum creatinine should be measured prior to each dose of Zoledronic acid Actavis and treatment should be withheld if renal function has deteriorated. In the clinical trials, renal deterioration was defined as follows: - For patients with normal baseline serum creatinine (< 1.4 mg/dl or < 124 micromol/l), an increase of 0.5 mg/dl or 44 micromol/l; - For patients with abnormal baseline creatinine (> 1.4 mg/dl or > 124 micromol/l), an increase of 1.0 mg/dl or 88 micromol/l. [...] Method of administration [...] In patients with mild to moderate renal impairment, reduced zoledronic acid doses are recommended (see section "Posology" above and section 4.4). Instructions for preparing reduced doses of Zoledronic acid Actavis Withdraw an appropriate volume of the concentrate needed, as follows: - 4.4 ml for 3.5 mg dose - 4.1 ml for 3.3 mg dose - 3.8 ml for 3.0 mg dose [...] Section 4.4 Special warnings and precautions for use [...] Renal insufficiency Patients with TIH and evidence of deterioration in renal function should be appropriately evaluated with consideration given as to whether the potential benefit of treatment with Zoledronic acid Actavis outweighs the

Safety issue	Agreed pharmacovigilance activities	Agreed risk minimisation activities
		possible risk. The decision to treat patients with bone metastases for the prevention of skeletal related events should consider that the onset of treatment effect is 2-3 months. Zoledronic acid, used as indicated in sections 4.1 and 4.2, has been associated with reports of renal dysfunction. Factors that may increase the potential for deterioration in renal function include dehydration, pre-existing renal impairment, multiple cycles of zoledronic acid and other bisphosphonates as well as use of other nephrotoxic medicinal products. While the risk is reduced with a dose of 4 mg zoledronic acid administered over 15 minutes, deterioration in renal function may still occur. Renal deterioration, progression to renal failure and dialysis have been reported in patients after the initial dose or a single dose of 4 mg zoledronic acid. Increases in serum creatinine also occur in some patients with chronic administration of zoledronic acid at recommended doses for prevention of skeletal related events, although less frequently. Patients should have their serum creatinine levels assessed prior to each dose of Zoledronic acid Actavis. Upon initiation of treatment in patients with bone metastases with mild to moderate renal impairment, lower doses of zoledronic acid are recommended. In patients who show evidence of renal deterioration during treatment, Zoledronic acid Actavis should be withheld. Zoledronic acid Actavis should only be resumed when serum creatinine returns to within 10% of baseline. Zoledronic acid Actavis treatment should be resumed at the same dose as that given prior to treatment interruption. In view of the potential impact of zoledronic acid on renal function, the lack of clinical safety data in patients with severe renal impairment (in clinical trials defined as serum creatinine ≥ 400 micromol/l or ≥ 4.5 mg/dl for patients with TIH and ≥ 265 micromol/l or ≥ 3.0 mg/dl for patients with cancer and bone metastases, respectively) at baseline and only limited pharmacokinetic data in patients with severe renal impairment at baseline (creatinine clearance < 30 ml/min), the use of Zoledronic acid Actavis is not

Safety issue	Agreed pharmacovigilance activities	Agreed risk minimisation activities
		recommended in patients with severe renal impairment. [...] Section 4.5 Interaction with other medicinal products and other forms of interaction Section [...] Caution is indicated when Zoledronic acid Actavis is used with other potentially nephrotoxic medicinal products. Attention should also be paid to the possibility of hypomagnesaemia developing during treatment. In multiple myeloma patients, the risk of renal dysfunction may be increased when Zoledronic acid Actavis is used in combination with thalidomide. [...] Section 4.8 Undesirable effects [...] The following are the important identified risks with zoledronic acid in the approved indications: Renal function impairment, osteonecrosis of the jaw, acute phase reaction, hypocalcaemia, ocular adverse events, atrial fibrillation, anaphylaxis. The frequencies for each of these identified risks are shown in Table 1. Tabulated list of adverse reactions The following adverse reactions, listed in Table 1, have been accumulated from clinical studies and post-marketing reports following predominantly chronic treatment with 4 mg zoledronic acid: Table 1 [...] Renal and urinary disorders Common: Renal impairment Uncommon: Acute renal failure, haematuria, proteinuria Description of selected adverse reactions: Renal function impairment Zoledronic acid, used as indicated in sections 4.1 and 4.2, has been associated with reports of renal dysfunction. Factors that may increase the potential for deterioration in renal function include dehydration, pre-

Safety issue	Agreed pharmacovigilance activities	Agreed risk minimisation activities
		existing renal impairment, multiple cycles of zoledronic acid or other bisphosphonates, as well as concomitant use of nephrotoxic medicinal products or using a shorter infusion time than currently recommended. Renal deterioration, progression to renal failure and dialysis have been reported in patients after the initial dose or a single dose of 4 mg zoledronic acid (see section 4.4). [...]
Patient with hepatic insuficiency	Routine pharmacovigilance	Information is included in labelling (SPC section 4.4) Section 4.4 Special warnings and precautions for use [...] Hepatic insufficiency As only limited clinical data are available in patients with severe hepatic insufficiency, no specific recommendations can be given for this patient population.

The CHMP, having considered the data submitted, was of the opinion that routine pharmacovigilance was adequate to monitor the safety of the product.

No additional risk minimisation activities were required beyond those included in the product information.

PSUR submission

The PSUR submission schedule should follow the PSUR schedule for the reference product, which currently is on a 1-yearly cycle until otherwise decided by the CHMP. The next data lock point for the reference medicinal product is 31 August 2012.

User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

3. Benefit-risk balance

This application concerns a generic version of zoledronic acid concentrate for solution for infusion (4 mg/5 ml). The reference product Zometa is indicated for the prevention of skeletal related events (pathological fractures, spinal compression, radiation or surgery to bone, or tumour-induced hypercalcaemia) in patients with advanced malignancies involving bone, and for treatment of tumour-induced hypercalcaemia (TIH).

No nonclinical studies have been provided for this application but an adequate summary of the available nonclinical information for the active substance was presented and considered sufficient. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient.

There are no bioequivalence studies submitted with this application, and this is not required under the provisions of the "Guideline on the Investigation of Bioequivalence" (CPMP/QWP/EWP/1401/98 Rev.1), as the test product is to be administered as an aqueous intravenous solution containing the same active substance as the currently approved product.

A benefit/risk ratio comparable to the reference product can therefore be concluded.

The CHMP, having considered the data submitted in the application and available on the chosen reference medicinal product, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Zoledronic acid Actavis in the prevention of skeletal related events (pathological fractures, spinal compression, radiation or surgery to bone, or tumour-induced hypercalcaemia) in patients with advanced malignancies involving bone, and in the treatment of tumour-induced hypercalcaemia (TIH) is favourable and therefore recommends the granting of the marketing authorisation

CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2) .

C.OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

Pharmacovigilance system
The MAH must ensure that the system of pharmacovigilance presented in Module 1.8.1. of the Marketing Authorisation is in place and functioning before and whilst the medicinal product is on the market.

Risk Management Plan (RMP)
The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in the Risk Management Plan presented in Module 1.8.2. of the Marketing Authorisation and any subsequent updates of the RMP agreed by the Committee for Medicinal Products for Human Use (CHMP).

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the European Medicines Agency.

PSURs

The PSUR submission schedule should follow the PSUR submission schedule for the reference medicinal product

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not applicable.