24 July 2014
EMA/631924/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Zoledronic acid Teva 4mg/100ml solution for infusion

International non-proprietary name: Zoledronic acid

Procedure No. EMEA/H/C/002439/X/0008

Note

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

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Background information on the procedure

Submission of the dossier

The applicant Teva Pharma B.V. submitted on 26 December 2013 an application for an extension of the Marketing Authorisation to the European Medicines Agency (EMA) for Zoledronic acid Teva solution for infusion 4 mg/100 ml, through the centralised procedure falling within the Article 19 (1) and Annex I (point 2 intend d) of the Commission Regulation (EC) No 1234/2008.

Teva Pharma B.V.is already the Marketing Authorisation Holder for Zoledronic acid Teva concentrate for solution for infusion 4 mg/5 ml (EU/1/12/771/001-006).

The indication for Zoledronic acid Teva solution for infusion 4 mg/100 ml is the same as that of Zoledronic acid Teva concentrate for solution for infusion 4 mg/5 ml:

Prevention of skeletal related events and treatment of tumour-induced hypercalcaemia (TIH).

The legal basis for this application refers to:

The application submitted is composed of administrative information and complete quality data. For this type of product, intravenous solution, no bioequivalence data are required for intravenous solutions according to the guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98.

Information on Paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Not applicable

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific Advice

The applicant did not seek scientific advice at the CHMP.

Licensing status

Zoledronic acid Teva has been given a Marketing Authorisation in the European Union on 16 August 2012.

Manufacturers

Manufacturers responsible for batch release

Pharmachemie B.V.
Swensweg 5
NL-2031 GA Haarlem
The Netherlands

Teva Pharmaceutical Works Private Limited Company
Táncsics Mihály út 82
HU-2100 Godollo
Hungary

Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP and the evaluation teams was:

Rapporteur: Filip Josephson, SE

The application was received by the EMA on 05 December 2013.

- The procedure started on 26 December 2013.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 17 March 2014.
- During the meeting on 22-25 April 2014 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 25 April 2014.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 23 May 2014.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 01 July 2014.
- During the meeting on 22-24 July 2014 the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting an extension of the Marketing Authorisation for Zoledronic acid Teva solution for infusion 4 mg/100 ml.

2. Scientific discussion

Introduction

The active substance in Zoledronic acid Teva, 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 Teva also helps to reduce the amount of calcium released into the blood.

The current application concerns a generic version of zoledronic acid solution for infusion (4 mg /100 ml). The reference product is Zometa. The applicant applied for the following indications which are the same as for the reference product:

- 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).

This application is an extension of marketing authorisation to include an additional pharmaceutical form: Solution for infusion. Zoledronic acid Teva 4 mg/100 ml solution for infusion is the same strength as that prepared by dilution of the currently approved/marketed Zoledronic acid Teva 4 mg/ 5 ml concentrate.

Quality aspects

Introduction

The medicinal product is presented as solution for infusion (4 mg /100 ml) of zoledronic acid as the active substance, intended for intravenous use.

The excipients, as listed in the SmPC section 6.1, are mannitol, sodium citrate, sodium chloride and water for injections.

The product is available in Cyclic Olefin Polymer (COP) plastic bottles closed by grey chlorobutyl/butyl rubber stopper and blue plastic flip-off cap.

Active Substance

The active substance used in the solution for infusion (4 mg /100 ml) is the same active substance as the one approved for the currently authorised presentation (concentrate for solution for infusion 4 mg/5 ml) and no new information has been presented.

Finished Medicinal Product

Description of the product and pharmaceutical development

The aim of the pharmaceutical development was to develop a diluted product of the concentrate for solution for infusion. This new pharmaceutical form was developed to facilitate administration to patients. This presentation is also authorised for the reference medicinal product Zometa.

The applied product has the same qualitative composition as Zometa 4 mg/5 ml concentrate for solution of infusion and Zometa 4 mg/100 ml solution for infusion except that the applied product contains sodium chloride and the reference products do not. A comparison of the physicochemical properties of the products (appearance, pH, osmolality, viscosity, impurities and assay) demonstrates essential similarity of the products.

Since the formulation is an aqueous intravenous solution containing the same active substance at the same concentration as the reference product no bioequivalence studies are required.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

The primary packaging is Cyclic Olefin Polymer (COP) plastic bottle, fitted with a chlorobutyl/butyl rubber stopper and aluminium cap fitted with blue plastic flip off disc.The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process is a standard process for parenteral formulations and consists of four main steps: dissolution, sterile filtration, filling and terminal moist heat sterilisation.

The required manufacturing parameters and ranges were determined during manufacturing process development and process validation.

Major steps of the manufacturing process have been validated by a number of studies. Validation of the manufacturing process has been performed on three commercial scale batches. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

Product specification

The release and shelf life specification includes tests and limits appropriate for this kind of dosage form for the following parameters: description (visual), clarity of solution (Ph.Eur), visible particles (Ph.Eur), colour of solution (Ph.Eur), osmolality (Ph.Eur), extractable volume (Ph.Eur), pH value (Ph.Eur), identification (In-house), assay (In-house), related substances (In-house), sub-visible particles (Ph.Eur), bacterial endotoxins (Ph.Eur) and sterility (Ph.Eur).

Batch analysis results from three commercial scale batches confirm consistency and uniformity of manufacture and indicate that the process is under control.

Stability of the product

Stability data of tree production scale batches of finished product stored under long term conditions for 12 months at 25 ºC / 60 % RH, under intermediate conditions for 12 months at 30 ºC / 65 % RH and for up to 6 months under accelerated conditions at 40 ºC / 75 % RH according to the ICH guidelines were provided.

The batches of Zoledronic acid Teva solution for infusion 4 mg/100 ml are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

The shelf life specifications are the same as for release and include a test for weight loss.

A photostability study was performed on one batch in accordance with the requirements of ICH Q1B. Results of the photo-stability studies demonstrate that Zoledronic acid Teva 4 mg/100 ml solution for infusion is not light sensitive.

In addition a freeze-thaw study with three cycles (<-15 °C/48 hours / +40 °C/48 hours) was performed for one batch with no significant changes were observed.

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

Adventitious agents

No excipients derived from animal or human origin have been used.

Discussion on chemical, pharmaceutical and biological 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 clinical use.

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 SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

Recommendation(s) for future quality development

Not applicable.

Non-clinical aspects

Introduction

The applicant presented justifications for not generating 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.

Ecotoxicity/environmental risk assessment

The proposed new pharmaceutical form, Zoledronic acid Teva 4 mg/100 ml, solution for infusion is intended to be marketed as alternative presentation to the currently marketed Zoledronic acid Teva 4 mg/5 ml concentrate for solution for infusion. The use of this product is not expected to increase the risk to the environment. In conclusion, it is acceptable that no new ERA is provided with this application.

Conclusion on the non-clinical aspects

No new non-clinical studies have been performed, and none are required for this type of application. There are no non-clinical issues that need to be addressed.

Clinical aspects

Introduction

This application is an extension of marketing authorisation to include an additional pharmaceutical form: Solution for infusion. Zoledronic acid Teva was granted marketing authorisation in 2012 for Zoledronic acid Teva 4 mg/ 5 ml concentrate for solution for infusion. The current extension of the marketing authorisation is for 4 mg/100 ml solution for infusion; it is the same strength as that prepared by dilution of the currently approved/marketed product. The applied product is to be administered as an aqueous intravenous solution containing the same active substance as the currently authorised product. The applied product also contains the same excipients, with the exception of sodium chloride, as the reference product. For this type of product, no bioequivalence studies are required according to the Guideline on the investigation of Bioequivalence (CHMP/QWP/EWP/1401/98 Rev. 1) and the applicant has submitted none.

No new pharmacodynamic studies were presented and no such studies are required for this application.

The indications applied for are in accordance with those of the originator.

Post-marketing experience

No post-marketing data are available for Zoledronic acid Teva 4m/100 ml.

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 CHMP received the following PRAC Advice on the submitted Risk Management Plan: The PRAC considered that the risk management plan version 4.1 is acceptable. The PRAC endorsed PRAC Rapporteur assessment report is attached.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 4.1 with the following content:

Safety concerns

Summary of safety concerns	
Important identified risks	• Osteonecrosis of the jaw (ONJ) • Hypocalcaemia • Renal impairment/renal failure • Acute phase reaction • Hypersensitivity reactions • Ocular adverse events

Summary of safety concerns	
	• Atrial fibrillation • Interstitial lung disease • Interaction with anti-angiogenic drugs
Important potential risks	• Atypical femoral fractures • Cardiac arrhythmias • Fracture healing impairment • Cerebrovascular adverse events • Focal segmental glomerulosclerosis • Potential interaction with nephrotoxic drugs • Medication errors • Off-label use in osteogenesis imperfecta
Missing information	• Races other than Caucasians • Use during pregnancy and lactation • Impact on fertility • Use in patients below 18 years of age • Patients with severe renal impairment • Patients with severe hepatic insufficiency

Pharmacovigilance plan

The PRAC noted that the MAH did not propose additional pharmacovigilance activities beyond routine.

The PRAC considered that routine pharmacovigilance is sufficient to identify and characterise the risks of the product.

The PRAC also considered that routine pharmacovigilance is sufficient to monitor the effectiveness of the risk minimisation measures.

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
IMPORTANT IDENTIFIED RISKS		
Osteonecrosis of the jaw (ONJ)	Labelling: Risk has been highlighted in the SmPC in section 4.4 *Special warnings and special precautions for use*, 4.5 *Interaction with other medicinal products and other forms of interaction*, and in section 4.8 *Undesirable effects*. Prescription-only medicine.	None
Hypocalcaemia	Labelling: Risk has been highlighted in the SmPC in sections 4.4 *Special warnings and precautions for use, 4.7 Fertility, pregnancy and lactation,* 4.8 *Undesirable effects* and in	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	section 4.9 *Overdose*. Prescription-only medicine.	
Renal impairment/ renal failure	Labelling: Risk has been highlighted in the SmPC in section 4.4 *Special warnings and special precautions for use*, 4.5 *Interaction with other medicinal products and other forms of interaction, 4.8 Undesirable effects and in section 4.9 Overdose.* Prescription-only medicine.	None
Acute phase reaction	Labelling: Risk has been highlighted in the SmPC in section 4.8 *Undesirable effects*. Prescription-only medicine.	None
Hypersensitivity reactions	Labelling: Risk has been highlighted in the SmPC in section 4.8 *Undesirable effects*. Zoledronic acid is contraindicated in patients with hypersensitivity to the active substance, to other bisphosphonates or to any of the excipients. Prescription-only medicine.	None
Ocular adverse events	Labelling: Risk has been highlighted in the SmPC in section 4.8 *Undesirable effects*. Prescription-only medicine.	None
Atrial fibrillation	Labelling: Risk has been highlighted in the SmPC in section 4.8 *Undesirable effects*. Prescription-only medicine	None
Interstitial lung disease	Labelling: Risk has been highlighted in the SmPC in section 4.8 *Undesirable effects*. Prescription-only medicine.	None
Interaction with antiangiogenic drugs	Labelling: Risk has been highlighted in the SmPC in section 4.5 *Interaction with other medicinal products and other forms of interaction*. Prescription-only medicine.	None
IMPORTANT POTENTIAL RISKS		
Atypical femoral fractures	Labelling: Warning in section 4.4 *Special warnings and special precautions for use* on the risk of atypical fractures of the femur and listed	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	as a class adverse reaction in Section 4.8 *Undesirable effects* of the SmPC. Prescription-only medicine.	
Cardiac arrhythmias	Labelling: Risk has been highlighted in the SmPC in sections 4.4 *Special warnings and precautions for use,* and 4.8 *Undesirable effects*. Prescription-only medicine.	None
Fracture healing impairment	In the absence of specific safety signals relating to fracture healing impairment the applicant does not propose any specific risk minimisation activities at this time. Prescription-only medicine.	None
Cerebrovascular adverse events	In the absence of specific safety signals relating to cerebrovascular adverse events the applicant does not propose any specific risk minimisation activities at this time. Prescription-only medicine.	None
Focal segmental glomerulosclerosis	In the absence of specific safety signals relating to focal segmental glomerulosclerosis the applicant does not propose any specific risk minimisation activities at this time. Prescription-only medicine.	None
Potential interaction with nephrotoxic drugs	Labelling: Risk has been highlighted in the SmPC in section 4.4 *Special warnings and special precautions for use*, 4.5 *Interaction with other medicinal products and other forms of interaction*, and in section 4.8 *Undesirable effects*. Prescription-only medicine.	None
Medication errors	The SmPC clearly states the medicinal product strength, indication, posology and method of administration (sections 4.1 and 4.2). There is a clear difference in appearance and labelling of the carton and vial/bottle for each pharmaceutical form (zoledronic acid 4 mg/5 ml concentrate for solution for infusion and zoledronic acid 4 mg/100 ml solution for infusion).	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Prescription-only medicine.	
Off-label use in osteogenesis imperfecta	Clinical trial results in the treatment of severe osteogenesis imperfecta in paediatric patients aged 1 to 17 years are described in the SmPC section 5.1 *Pharmacodynamic properties*. Drug is not indicated in osteogenesis imperfecta. Prescription-only medicine.	None
MISSING INFORMATION		
Races other than Caucasians	In the absence of specific safety signals relating to zoledronic acid use in races other than Caucasians the applicant does not propose any specific risk minimisation activities at this time. Prescription-only medicine.	None
Use during pregnancy and lactation	Zoledronic acid is contraindicated in breastfeeding women. Information is given in section 4.6 *Fertility, pregnancy and lactation*. Prescription-only medicine.	None
Impact on fertility	Information is given in section 4.6 *Fertility, pregnancy and lactation*. Prescription-only medicine.	None
Use in patients below 18 years of age	Labelling: Information is given in sections 4.2 *Posology and method of administration,* and 5.1. The safety and efficacy of zoledronic acid in children aged 1 year to 17 years have not been established. Currently available data do not support drug use in this population; potential use will be followed-up routinely. Prescription-only medicine.	None
Patients with severe renal impairment	Labelling information presented in the SmPC sections 4.2 *Posology and method of administration* and 4.4 *Special warnings and precautions for use*. Prescription-only medicine.	None
Patients with severe hepatic insufficiency	Labelling information presented in the SmPC section4.4 *Special warnings and precautions for use*.	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Prescription-only medicine.	

Product information

User consultation

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.*

Benefit-Risk Balance

Neither non-clinical studies nor clinical studies have been provided for this line extension application, which is considered acceptable. An adequate summary of the available non clinical information for the active substance was presented in the application for the original dosage form (Zoledronic acid Teva 4 mg/ 5 ml concentrate for solution for infusion, approved in August 2012), which is considered sufficient for this application as well. 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 current state of knowledge concerning the safety and efficacy of the reference product has been evaluated by means of a literature search and there is no data to indicate any likely change to the benefit/risk ratio. The applicant's clinical overview on the clinical aspects presented in the application for Zoledronic acid Teva 4 mg/5 ml concentrate for solution for infusion based on information from published literature is considered sufficient for this application as well. However, there are still some minor comments on the product information (see below).

The application is composed of satisfactory quality data. No additional non-clinical or clinical data have been provided, which is satisfactory for this line extension; bioequivalence data are not required for this intravenous aqueous solution. A satisfactory update of the RMP has been submitted by the Applicant. A benefit/risk ratio comparable to the reference product can therefore be concluded.

Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Zoledronic acid Teva solution for infusion 4mg/100ml in the prevention of skeletal related events and treatment of tumour-induced hypercalcaemia (TIH) is favourable and therefore recommends the granting of the extension of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

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

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this medicinal product if the product is included in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83 and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.