21 May 2015
EMA/CHMP/383288/2015
Procedure Management and Committees Support Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Zometa

ZOLEDRONIC ACID

Procedure no: EMEA/H/C/000336/P46/040

Note

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

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Assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No 1901/2006, as amended

Zometa

International non-proprietary name: Zoledronic acid

Procedure no.: EMA/H/C/000336/P46 040

Marketing authorisation holder (MAH): Novartis Europharm Ltd

Rapporteur:	Christian Schneider (DK)
Start of the procedure:	22nd March 2015
Date of this report:	21st April 2015
Deadline for CHMP member's comments:	6th May 2015
Date of the Rapporteur's final report:	11th May 2015
Need for plenary discussion	No

Administrative information

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1. Introduction

On February 19, 2015, the MAH submitted an English summary of the clinical study report of a completed Japanese study including one paediatric patient for Zometa, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

Article 46 of Regulation (EC) No 1901/2006 requires that any marketing authorisation holder sponsored study which involves the use in the paediatric population of a medicinal product covered by a marketing authorization, whether or not they are conducted in compliance with an agreed paediatric investigation plan, is to be submitted to the competent authority.

In a recent review of the requirements of the Paediatric Regulation, Novartis has prepared aremediation action to ensure that all paediatric data is submitted in accordance with Article 46 of the Paediatric Regulation. In this context and in accordance with Article 46 of the Paediatric Regulation we would like to submit the data of a paediatric patient included in study CZOL446DJP01 which was conducted solely in Japan. Study CZOL446DJP01 is a Novartis-sponsored Japanese study and was conducted for purposes of providing postmarketing surveillance data in Japanese patients to comply with post-marketing reuirements. One patient in the study was a paediatric patient < 18 years. The study is not linked to other paediatric studies which have been or will be the subject of other Article 46 submissions.

As this study has only been conducted in Japan with limited contribution of paediatric patients a complete English translation of the clinical study report has not been submitted.

Also, as only one paediatric patient was included in this post-marketing surveillance study, and that no AE was reported for this patient, only a summary of the clinical study report in English and a line listing including the single paediatric patient are provided in stead of short critical expert overview as critical analysis of the data for the paediatric patient is not warranted.

2. Scientific discussion

2.1. Information on the development program

N/A

2.2. Information on the pharmaceutical formulation used in the study

N/A

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a summary of final report for:

- CZOL446DJP01, the MHLW (Ministry of Health, Labour, and Welfare) mandated drug use observational investigation of Zometa

2.3.2. Clinical study

CZOL446DJP01, The MHLW (Ministry of Health, Labour, and Welfare) mandated drug use observational investigation of Zometa

Description

Methods

Objective(s)

Primary objective is to confirm the safety and efficacy for Zometa(zoledronic acid) under the actual medical practice.
Secondary objective is to confirm the efficacy of Zometa under the actual medical practice.

Study design

Japanese post marketing surveillance. The surveillance is required by the local regulation.
Multiple institution, un-blind, no-control, multiple dose, all patient surveillance.

Prior to the initiation of the surveillance, the contract for the surveillance is concluded between NPKK (Novartis Pharma KK) and the medical institution. Drug is supplied to the medical institutions after confirmation of the contract by NPKK. The investigators should send the registration form for the patients prescribed Zometa to the central enrollment system (CRO). The investigators describe the safety and efficacy data into the CRFs as soon as completion of observation period, and NPKK collects CRFs from the investigators. NPKK carries out the statistical analysis and prepare the interim report, and it is submitted to PMDA (One of health authority) annually.

Study population /Sample size

All Patients treated with Zometa for hypercalcemia due to malignant tumor

Number of planned subjects: All patients (More than 1000 patients)
Number of subjects registrated: 1111 patients
Number of subjects for safety analysis: 1073 patients
Number of subjects for efficacy analysis: 771 patients

Study period

From Oct 22nd, 2004 to Mar 22nd, 2007. (From approval date to after 2.5 years)

Treatments

Outcomes/endpoints

Measurements

- Patient's background
- Content of just before treatment for hypercalcemia
- Drug dose, infusion time, quantity of dilution
- Concomitant medications
- Condition of a month after the last dosage

- Laboratory test including Ca, Albumin, BUN and creatinine
- Adverse events
- Priority items (Hypocalcaemia, Renal impairment)

Safety assessments

- Appearance related side-effects and infections (Type and appearance rate)
- Appearance related side-effects every patient's background
- Appearance related serious adverse events (Type and appearance rate)

Efficacy assessments

- Normalization rate of calcium level is determined by the investigator.

Results

Safety results

The incidence of side effects in this use-result survey was 8.85% (95/1073 patients), and was lower compared to the incidence of side effects until the approval, 84.62% (22/26 patients). This is probably due to very low number of subjects (26 patients) in the clinical study, and due to more detailed findings collected as adverse events through Source Data Verification (SDV) by clinical research associates (field monitors), than in general practices.
The common side effects by System Organ Classes and incidence were; Metabolism and nutrition disorders in 3.17% (34/1073 patients), Investigations in 2.80% (30/1073 patients), and General disorders and administration site conditions in 2.14% (23/1073 patients).
Although the incidence of the System Organ Classes was lower compared to the status until the approval, the trend of side effects was similar.
Among side effects which are called for attention in the section (1) Clinically significant side effects of the package insert, no side effects were notably high in incidence compared to the occurrence until the approval.
The side effects found in this use-result survey but not found until the approval were; osteomyelitis, periodontitis, pneumonia, cancer pain, anaemia, disseminated intravascular coagulation, hypoalbuminaemia, hypocalcaemia, hypoproteinaemia, decreased appetite, depression, eating disorder, optic neuritis, pericardial effusion, pleural effusion, diarrhoea, rash, arthralgia, back pain, pain in extremity, pain in jaw, renal disorder, renal failure, renal impairment, calcinosis, chest pain, malaise, Albuminemia in blood, blood calcium increase, blood creatinine decreased, blood lactate dehydrogenase increased, blood potassium increased, blood sodium increased, blood urea increased, C-reactive protein increased, thrombocytopenia, weight decreased, and leukopenia. The incidence of the above side effects was all low (0.09% to 0.37%). While, the side effects found until the approval but not found in this use-result survey were: altered state of consciousness, hypoaesthesia, pulmonary oedema, blister, eczema, haematuria, polyuria, beta 2 microglobulin urine increased, blood potassium decreased, blood urine present, haemoglobin decreased, and blood phosphorus decreased. The side effects found in this use-result survey which are listed in Precautions were; hypocalcaemia (2.70%), and blood urea increased (1.12%, 12 cases).
No notable issues were found as change in trend of side effects or common incidence of side effects unexpected from Precautions. No remarkable issues were found as incidence of significant side effects listed in the package insert are commonly found, compared to the data to the approval.

In patients with renal impairment, no new findings requires attention, however, careful administration should be continued while observing their conditions especially in patients with serious renal disorder. No other issues were found in side effects in elderly patients or patients with hepatic function disorder (data were not collected for pediatric, pregnant or nursing patients).

Efficacy results

Investigated 771 patients as efficacy analysis set, and 79.90% of patients were determined by the investigator as to have achieved complete response of corrected serum calcium level. This was comparable to the efficacy in 84.0% of patients determined to have achieved complete response of corrected serum calcium level in a Phase II study for approval in Japan (Study 1201) in patients with hypercalcemia of malignancy.

2.3.3. Conclusion on clinical aspects

1091 patients were enrolled in the surveillance.
Main side effects were Hypocalcaemia 2.70% (29 cases), Blood urea increased 1.12% (12 cases), Blood creatinine increased 1.03% (11 cases), and Pyrexia 1.77% (19 cases).

3. Rapporteur's overall conclusion and recommendation

Only one paediatric patient (age: 16 years, male) was included in the post-marketing surveillance study above. No AEs were reported for this patient.

Thus the results from this study does not change the benefit-risk profile for paediatric patients

☒ **Fulfilled:**

No regulatory action required.