London, 12 October 2017
EMA/607273/2017
Committee for Medicinal Products for Human Use (CHMP)

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

Xolair

omalizumab

Procedure no: EMEA/H/C/000606/P46/061

Note

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

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8613
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

Table of contents

1. Introduction

On July 12:th, 2017, the MAH submitted a completed paediatric study for Xolair, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

Novartis has completed a non-interventional post-marketing surveillance study CIGE025A1402 entitled, “Specified Drug Use survey in all Japanese patients with bronchial asthma receiving Xolair for s.c. injection 75 mg/150 mg.” The aim of this study was to collect safety and efficacy data on long-term use of omalizumab in actual medical practice. This survey was conducted in Japan and registered a total of 3,893 patients. 25 patients in the study were children.

A short critical expert overview written by a Novartis employee has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that CIGE025A1402 is a stand alone study.

2.2. Information on the pharmaceutical formulation used in the study

Xolair, as approved was used in this study.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- CIGE025A1402 entitled, “Specified Drug Use survey in all Japanese patients with bronchial asthma receiving Xolair for s.c. injection 75 mg/150 mg”; last patient last visit on 25-Jan-2017.

2.3.2. Clinical study

CIGE025A1402

Description

Study CIGE025A1402 was a Non Interventional Study conducted in Japanese patients with bronchial asthma receiving Xolair 75 mg and 150 mg powder for solution for injection (lyophilized form). The aim of this study was to collect safety and efficacy data on long –term use of omalizumab in actual medical practice.

Methods

Objective(s)

The objective of the survey was to collect safety and efficacy data on long-term use of omalizumab in actual medical practice, to understand any related issues, and to examine Xolair's suppressive effects on exacerbation of asthma.

Study design

The Drug-Use survey was conducted in the setting of actual clinical practice using a central registration system with a 1-year observation period. (A follow-up survey has been conducted to verify whether treatment status is continued and to collect information related to AEs of malignant tumor at the 2nd and 3rd year in patients continuing Xolair treatment for at least 1 year.)

The standard observation period (duration of treatment) was 1 year. If no improvement was observed in asthma symptoms as the efficacy assessment at Week 16, the treatment with Xolair was discontinued and the data of one-year-observation was collected.

Study population

The target population for this survey study consisted of patients with poorly controlled bronchial asthma with refractory asthma symptoms despite standard of care.

Outcomes/endpoints

Global evaluations of treatment effectiveness (GETE)

Adverse events

Other survey items for which no results are reported by the MAH included; patient characteristics, status of Xolair® use, evaluation of continuous treatment/long-term administration, treatment status of asthma (from 6 months prior to Xolair treatment to 1 year after the treatment), treatment for asthma attack, other concomitant medications, clinical course (asthma symptoms, pulmonary function test, events related to asthma exacerbation, concomitant allergic diseases), laboratory values, discontinuation/withdrawal.

Results

Recruitment/ Number analysed

A total of 3,893 patients participated in this study. Out of the 3,893 patients, Case Report Forms (CRFs) were not collected in 220 patients. These missing survey results were due to a variety of reasons, including physician's refusal to complete such survey or changing practice location, among others. Therefore the database includes 3,673 patients, of whom 2,123 patients (59%) completed the study. 1,497 patients (41%) discontinued prematurely from the study: the most frequent reasons recorded for discontinuation were: inadequate response (471/1,497), adverse event (288/1,497) and symptom improved (247/1,497).

In the age group less than 18 years, 26 patients were enrolled and 25 patients were included in the safety analysis set (one patient with off-label use which is out of the scope for this survey study was removed from safety analysis set). 12 patients discontinued prematurely from the study, however no cases of discontinuation were due to safety reasons ("Symptom improved" in 5 patients, "Economic reason" in 1 patient, "Lost to follow-up" in 1 patient, "Moving" in 1 patient, "Patient decision" in 1 patient, and "Other" in 3 patients).

Efficacy results

The GETE by physicians using a 5-grade scale were evaluated at each time point and at final evaluation. Patients who discontinued treatment < 2 months after initiation, and for whom GETE was not collected at discontinuation were not included in the tabulation for GETE, because there were no

usable data for them. As a result, GETE was analyzed for 3,585 patients in the entire population. The evaluations at the final observation were “Excellent” in 15% (553/3,585), “Good” in 34% (1,222/3,585), “Moderate” in 24% (860/3,585), “Poor” in 18% (660/3,585) and “Worsening” in 3% (114/3,585). The effectiveness rate was calculated by defining those with scores of either “Excellent” or “Good” as being considered “effective” was 50% (1,775/3,585).

In the patient group aged less than 18 years, the evaluations at the final observation were “Excellent” in 44% (11/25), “Good” in 28% (7/25), “Moderate” in 20% (5/25), “Poor” in 4% (1/25) and “No Worsening” case. The effectiveness rate in the patient group aged less than 18 years was 72% (18/25). Due to the small number of patients in the age group less than 18 years there are no other subgroup efficacy data in these patients.

Safety results

In the entire study population, the most frequently reported AEs were asthma (11%), nasopharyngitis (5%), pneumonia (2%), and bronchitis (2%). Adverse drug reactions (ADRs: AEs suspected to be related to Xolair) were reported in 292 patients (8%).

There were no ADRs with an incidence > 1%. The most frequently reported ADRs were malaise (0.9%), urticaria (0.7%), dizziness (0.5%), pyrexia (0.5%), and rash (0.5%) which are expected to occur due to administration of Xolair.

The frequently reported (> 1%) SAEs were asthma (10%) and pneumonia (1.6%). SAEs suspected to be related to Xolair were reported in 36 patients, and the most common of these SAEs were anaphylactic reaction (4), asthma (3), muscular weakness (3), hypersensitivity (2), and nausea (2).

A total of 62 death cases out of 3,620 cases were reported in this study. The most common causes of death cases included: pneumonia (14 deaths) followed by asthma (8 deaths), cardiac failure acute (5 deaths), and sepsis, death (cause unknown), and myocardial infarction (3 deaths). All death cases were reported by the investigator as not suspected to be related to Xolair except two cases: myocardial infarction and uterine cancer (see below summary).

Myocardial infarction (75 year old, female): Patient had a medical history of eosinophilic granulomatosis with polyangiitis (EGPA), conjunctivitis allergic, dementia, hypertension, and trigeminal neuralgia. The patient suffered from a myocardial infarction 5 months after the start of Xolair treatment and died. The physician assessed the causality with Xolair for myocardial infarction as uncertain.

MAH’s assessment: The patient has concurrent allergic granulomatous angiitis/ eosinophilic granulomatosis with polyangiitis (EGPA). In the last stage of EGPA (vasculitis), the most serious complication of the vasculitic stage is heart disease, which is the cause of nearly half of all deaths in patients with EGPA. Among heart disease-related deaths, the most usual cause is inflammation of the heart muscle caused by the high level of eosinophils, although some are deaths due to inflammation of the arteries that supply blood to the heart or pericardial tamponade. Blood clots may develop within the damaged arteries in severe cases, which are followed by infarction and cell death, or slow atrophy. Therefore MAH considered this case as confounded by EGPA.

Uterine cancer (71 year old, female): Patient had a medical history of rheumatoid arthritis (Enbrel, Rheumatrex, and Prednisolone for about 2 years), osteoporosis (Bonalon for about 2 years) and rhinitis allergic. Uterine cancer (Stage IIIB) was diagnosed 9 months after start of Xolair treatment. The patient died 5 months after the diagnosis was made. The physician assessed the causality with Xolair for uterine cancer as “uncertain”.

MAH's assessment: Time-to-onset between Xolair start and uterine cancer diagnosis is 9 months, a time frame which is not plausible for solid tumors. It should be noted that the patient additionally was being treated for 2 years with Etanercept, a drug which is associated with an increased risk of malignancies. Considering this information, the MAH assessed this case as being confounded by etanercept.

In the age group less than 18 years, AEs were reported in 8 patients. The most common event was nasopharyngitis (3 cases). In the patient group aged less than 18 years, ADRs were reported in 2 patients (1 episode each of headache, rash generalized, and menstruation irregular), all non-serious events. An SAE of "asthma" requiring hospitalization was reported in one patient. No death cases were reported in this age group.

Table 3-1 Adverse events in patients aged less than 18 years (Study CIGE025A1402)

	N=25	
Number of patients with AE	8 (32.00%)	
Number of episodes of AE	19	
Incidence of AEs (episodes) by type (%)[*1]		
Infections and infestations	6	(24.00)
Nasopharyngitis	3	(12.00)
Gastroenteritis	1	(4.00)
Oral candidiasis	1	(4.00)

	N=25	
Haemophilus infection	1	(4.00)
Herpes simplex	1	(4.00)
Impetigo	1	(4.00)
Nervous system disorders	2	(8.00)
Headache	1	(4.00)
Loss of consciousness	1	(4.00)
Syncope	1	(4.00)
Respiratory, thoracic and mediastinal disorders	2	(8.00)
Asthma	1	(4.00)
Oropharyngeal pain	1	(4.00)
Gastrointestinal disorders	1	(4.00)
Diarrhoea	1	(4.00)
Vomiting	1	(4.00)
Skin and subcutaneous tissue disorders	1	(4.00)
Rash generalised	1	(4.00)
Reproductive system and breast disorders	1	(4.00)
Menstruation irregular	1	(4.00)
General disorders and administration site conditions	1	(4.00)
Pyrexia	1	(4.00)
Investigations	1	(4.00)
Weight increased	1	(4.00)

MedDRA/J VERSION 19.1

*1 Percentage was calculated per number of patients in the survey.

Multiple episodes of the same event (PT) in the same patient were counted as 1 episode.

AEs are shown in the following order: Internationally agreed order for SOCs (ascending) → incidence of PTs (descending) → PT codes (ascending).

These safety findings are in line with the known and well defined safety profile of Xolair. No new safety findings were identified in either the entire population or in the pediatric population.

2.3.3. Discussion on clinical aspects

The results of this trial raised no new safety concerns and do not change the overall risk/benefit profile of Xolair® (omalizumab). There are no proposed changes to the existing Product information.

3. Rapporteur's overall conclusion and recommendation

The study report for Study CIGE025A1402 has been provided as requested according to Article 46 of Regulation (EC) No1901/2006, as amended. There were no unexpected findings.

☒ Fulfilled:

No regulatory action required.

☐ Not fulfilled:

4. Additional clarification requested

NA