EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Procedure Management and Committees Support Division

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/P46/046

Note

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

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Final Rapporteur's Assessment Report for the Post-Authorisation Measure EMEA/H/C/606 P46 046

Xolair

International non-proprietary name: omalizumab

Procedure No. EMEA/H/C/606 P46 046

Marketing authorisation holder: Novartis Europharm Ltd, United Kingdom

Date of this report:	22 October 2015
Deadline for comments:	09 November 2015

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1. Introduction

This report covers the following post-authorisation commitments undertaken by the MAH:

On 14 Aug 2015 the MAH submitted the study IGE025ATW01 a prospective, open label, observational, non-interventional, multicenter, 52-week study to assess the efficacy and safety of Xolair in patients with uncontrolled severe persistent asthma. The study included one pediatric subject why the data is submitted in accordance with Article 46 of Regulation (EC) No1901/2006, on medicinal products for paediatric use.

Xolair is approved as add-on therapy to children 6-12 years of age to improve asthma control in patients with severe persistent allergic asthma who have a positive skin test or in vitro reactivity to a perennial aeroallergen and frequent daytime symptoms or night-time awakenings and who have had multiple documented severe asthma exacerbations despite daily high-dose inhaled corticosteroids, plus a long-acting inhaled beta2-agonist. A similar indication is approved for adolescents and adults.

1.1. Steps taken for the assessment

Submission date:	14 August 2015
Start of procedure:	21 September 2015
CHMP Rapporteur's preliminary assessment report circulated on:	22 October 2015
CHMP Rapporteur's updated assessment report circulated on:	n/a
CHMP opinion:	19 November 2015

2. Assessment of the post-authorisation measure PAM P46 046

2.1. Purpose of submission

Study [IGE025ATW01 (EXACT)] (last patient last visit on 17-Jun-2014) was a prospective, open label, observational, non-interventional, multicenter, 52-week study to assess the efficacy and safety of Xolair in patients with uncontrolled severe persistent asthma. This study targeted a specific patient population with asthma of allergic nature and excluded patients whose asthma was associated/secondary to other clinical and non-allergic conditions and was conducted in patients ≥ 12 years of age, from 8 centers in Taiwan.

The primary objectives were to evaluate the effectiveness of Xolair at 12 weeks based on improvement of asthma control status composed of asthma control test (ACT), reduction of oral or inhaled corticosteroid dose and reduction of asthma related events.

The secondary objectives were

- To assess the safety and tolerability based on the incidence of AEs and SAEs
- To observe treatment persistence over the period of 52 weeks.
- To collect reasons for non-persistent treatment (a treatment interruption over 12 weeks or discontinuation of treatment was regarded as non-persistence of Xolair)
- To evaluate the effectiveness of Xolair on pulmonary function and exhaled nitric oxide response at 12 and 52 weeks in persistent and non-persistent patients
- To evaluate clinical effectiveness of Xolair at 52 weeks based on improvement of asthma control status in persistent and non-persistent patients

Seventy-eight participants were enrolled in the trial and all received Xolair. A treatment interruption over 12 weeks, or discontinuation of treatment, was regarded as non-persistence of Xolair. The non-persistence group consisted of one third of the patients. The results of the persistence group and the non-persistence group were compared in the evaluation of efficacy and safety.

The results of this study are now submitted to the CHMP according to Article 46 of Regulation (EC) No 1901/2006 since it includes one pediatric patient.

CHMP comment:

Several endpoints are listed as primary objectives of this study. The subjects that were non-persistent were used for comparison of data between groups. The most common reason for non-persistence was treatment interruption >week 12 (23/26). The study design makes the results difficult to interpret as the non-persistence group includes patients withdrawing from treatment for different reasons, some of which possibly linked to lack of efficacy.

2.2. Efficacy

The overall mean ACT score was 16.0 ± 5.02 points at baseline in the ITT population. There were increases in the mean change in ACT score from baseline to weeks 12 and 52 ($p<0.001$)

During the 52 weeks of observation, the incidence of asthma related events was 23.0%. The definition of asthma related events was unscheduled visits in healthcare due to asthma exacerbation. The most frequent event was emergency room visits. The incidence of at least one asthma related event was 21.6% for the persistence group and 26.1% for the non-persistence group.

At week 52, a mean increase of 8.0 ± 54.19 L/min in Peak Expiratory Flow (PEF) was observed in the ITT population.

CHMP comment:

One of the endpoints stated as primary was reached as a significant increase in the ACT score from baseline throughout the study was recorded. Instead of the reduction of corticosteroid dose the MAH present data from lung function tests but there was no significant effect on these parameters. Data on the effect on oral or inhaled corticosteroids could not be found in the study report.
The presentation of study data appears incomplete and is thus difficult to interpret.

2.3. Safety

There were 251 AEs that occurred in 57 patients (73.1%). Sixteen AEs occurred in ten patients (12.8%) which were judged to be related to the study treatment. The most commonly reported SAE was asthma exacerbation. Other SAEs reported included pneumonia, septic shock, infectious diarrhea, congestive heart failure, acute hepatitis, unstable angina, rib fracture and death.
One patient died in the none-persistence group. The death was not considered related to study medication.

2.4. Pediatric summary

One pediatric patient was enrolled in this trial: patient 07-002 was a 13 year old male, who completed the study. The patient had an asthma exacerbation, which was reported as an SAE for which he was hospitalized and the patient also had 3 other asthma exacerbations reported as moderate, which were not reported as SAEs. None of the exacerbations were suspected to be related to the study drug.

2.5. Overall conclusion

Effect on one of the primary objectives, the ACT score, was shown in this study (IGE025ATW01) in the ITT population. Given the minimal amount of pediatric data, no new efficacy conclusions can be drawn in the pediatric group. There are no new safety concerns and no changes to the benefit/risk profile of Xolair.

CHMP comment: The MAH has presented paediatric data as requested in legislation. Only one paediatric patient was included in this study why no conclusion can be drawn on efficacy. Safety was adequately documented and there were no unexpected findings. The study report as such gives raise to several questions and no firm conclusions could be drawn on efficacy. Nevertheless, considering that this PAM is submitted in accordance with Article 46, issues related to the adult population included in the study are not pursued.

3. CHMP overall conclusion

3.1. Overall conclusion

The presented data does not change the benefit risk for omalizumab in the paediatric approved indications. No changes are warranted in the SmPC.

3.2. Recommendation

No further action required.

☒ PAM fulfilled (all commitments fulfilled) - No further action required

☐ PAM not fulfilled (not all commitments fulfilled) and further action required: