7 November 2014
EMA/649874/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report under Article 46

FLUENZ

International non-proprietary name: influenza vaccine (intranasal, live attenuated)

Procedure No: EMEA/H/C/001101/P46 028.1

Note

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

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1. Introduction

In Europe, Influenza vaccine live intranasal (Fluenz) has been approved for use in eligible children from 2 through 17 years of age and was expected to first be available for use in the EU during the 2012-2013 influenza season. The study MIMA-162 was a FDA requirement to expand the data describing the safety profile of FluMist in children < 5 years of age.

The final results of the study have been assessed by CHMP in January 2013 and a list of questions has been issued. The present report is assessing the answers provided by the MAH.

2. Assessment

1 / The MAH should further specify how main respiratory events (asthma, wheezing, sleep apnea) were validated and what diagnostic criteria have been used.

MAH response:

MA162 was an observational study of postvaccination medically-attended events. Given the large study population and the many different types of events that were investigated, it was not possible to implement validation procedures to evaluate cases on an individual basis. Instead, the study relied on extraction of diagnoses as coded by healthcare providers practicing within the Kaiser Permanente system and standardized algorithms. The same procedures were applied to LAIV recipients and controls: bias resulting from any ascertainment flaw would be balanced between the study groups.

Diagnoses were extracted from medical records using ICD9 codes as well as "write-in" diagnoses. At the time of the study, the medical record was not fully automated. Health care practitioners at Kaiser Permanente Northern California (KPNC) could check a box or write in a diagnosis that was later scanned. These diagnoses were later manually classified by the KPNC study team under supervision of the principal investigator. Codes searched for asthma were the ICD9 codes 493.* (asthma), or the write-in terms "asthma", "RAD", "RAWD", or "REACTIVE AIRWAY". The codes searched for wheezing were ICD9 code 786.07, or a write-in term including "wheez"; write-in terms were reviewed case by case, largely to dismiss false-positives, such as "Abnormal findings on Radiological examination." ICD9 codes make up the vast majority of events: 97.6% of asthma events were identified with an ICD9 code versus 2.4% identified with write-in terms. The rate of sleep apnea was different between cohorts in the hospital setting only: cases were identified with ICD9 code 327.23 (obstructive sleep apnea). Medical record review of each case determined that these children were being vaccinated with FluMist at pre-operative examinations for elective tonsillectomy and adenoidectomy surgery.

The Vaccine Study Center utilizes the clinical databases and electronic medical records of Kaiser Permanente Health Plan. These are not claims, but doctor's office visits, hospitalizations in the plan, or any other encounters of KPNC enrollees with health care practitioners. These databases and systems are thoroughly validated within the Kaiser Permanente system, and are utilized for patient care and management, operational quality assurance, billing, and as a secondary use for research efforts. The Vaccine Study Center at KPNC has regularly used the data for numerous pre- and post-licensure studies since its founding in the early 1990s.

CHMP comments: *The MAH specified study outcomes diagnostic criteria. No procedure was planned to validate study outcomes. Each write-in term was reviewed. Issue resolved*

2/ Although subjects judged to have a prior history of asthma disease were excluded from the study, the percent of FluMist recipients having any prior visits coded as asthma was 4.5%, compared to their matched controls of 10% to 11% for unvaccinated and TIV controls. The MAH should precise the mean time of occurrence of prior asthma visits (within 12 months, more than 12 months prior).

Moreover the MAH should provide additional analyse, focusing on asthma and wheezing events, with exclusion of patients with prior asthma visit during the previous year.

MAH response:

All Kaiser patients are classified according to a propriety software, DxCG, which identifies underlying morbidity and classifies patients according to the expected costs to the health plan in the following year, according to prior medical history. A section of DxCG classifies asthmatics, using a combination of numbers of visits, visit settings (emergency room, physician's office visit…) and medications. A person is identified as asthmatic with a combination of visits and medication. This was the group that was excluded from the study.

For the main study, we did not exclude KPNC enrollees with only one prior visit with a coded diagnosis of wheezing or asthma, as most children in this category would not be considered as having asthma.

However, we did a separate asthma/wheezing analysis in which we excluded all subjects with prior asthma visit to investigate incident cases of asthma only. This is the analysis presented in section 12.2.4.2 of the Clinical Study Report that indicates a lower risk of incident asthma or wheezing events in FluMist recipients.

The dates of asthma visits prior to vaccination or index date were not saved in the study data sets, so that we can not present the distribution of the time of occurrence of prior asthma visit.

CHMP comments: *MAH answers are noted. Issue resolved.*

3/ According to the company, 191 influenza cases were reported in FluMist recipients during the 2009-2010 H1N1 influenza pandemic season. Among them, it would be interesting to known, if possible, the number of influenza cases due to influenza A virus subtype H1N1.

MAH response:

Diagnoses were clinical, based on symptoms rather than testing. KPNC tests did not determine strain subtype.

However, all diagnoses were established within 42 days after vaccination or index date. During the study period, all swab specimens region-wide were type A, and in California only 2009 pandemic H1N1 was circulating so it is likely that all cases were due to the 2009 pandemic H1N1 strain.

CHMP comments: *The MAH response is acceptable.*

4 / Based on the reported information, no complete assessment can be performed with this case of Kawasaki Disease. The MAH should request more information concerning the follow-up of this case.

MAH response:

Please find below the patient's narrative:

As noted in the study report, on 08 Dec 2009, a 25-month-old male subject received a single dose of FluMist. No medical history or concomitant medications were reported. On 01 Jan 2010, the subject was traveling in China and developed high fever of 102°F to 104.3°F which lasted 2 days. On 04 Jan 2010, he had red eyes, rash in the body, swollen hands and feet, purple-red lips, and "strawberry tongue." The subject was not eating. On the same day, he went to see a doctor; however, the medication (not specified) did not alleviate the symptoms. On 06 Jan 2010, 29 days post administration of FluMist the subject went to the hospital, was diagnosed with Kawasaki disease and hospitalized. He improved after several days of treatment and was discharged from the hospital on 15 Jan 2010. The outcome of the event was ongoing. The investigator assessed the Kawasaki's disease as not related to FluMist. The sponsor also assessed the Kawasaki's disease as not related to FluMist.

Additional follow-up information was extracted from the medical record on 07 Feb 2013. The patient returned to the US on 09 Jun 2010 and was seen at Kaiser Permanente the following day for a recheck. Patient was well at this examination and a referral to cardiology was made.

In the pediatric cardiology appointment of 23 July 2010 it is stated that according to his parents (via interpreter), the patient has been doing well since the episode, without fevers or, rash. They deny any cardiovascular symptoms such as shortness of breath, tachypnea, excessive diaphoresis, cyanosis, exercise intolerance, chest pain, palpitations, or syncopal episodes. His growth and development have been normal. He has no other medical problems and is currently on no medications. The cardiovascular examination and EKG on this date were normal. His echocardiogram was also normal. In short, the evaluation found no evidence of heart disease or sequelae of his bout with Kawasaki Disease 6 months prior. He left with no restrictions to his activities. No follow-up studies were scheduled.

CHMP comments: *From the reported symptoms (especially the short duration of fever<5 days), it is not clear that this is a true confirmed case of KD. Because of a lack of information regarding results from infectious work up, no complete assessment can be performed with this case of KD. Moreover, given the latency period between immunization date and onset of fever (24 days), the assessor considers that the causal association between the event and Flumist immunization cannot be totally ruled out.*

III / CHMP conclusion

The MAH answered the CHMP requests for clarifications.

Recommendation

☒ **Fulfilled**

No further action required.