15 November 2012
EMA/376628/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Aflunov

Common name: prepandemic influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted)

Procedure No.: EMEA/H/C/002094/II/0007/G

Note

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

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1. Background information on the procedure

1.1. Requested Group of variations

Pursuant to Article 7.2(b) of Commission Regulation (EC) No 1234/2008, Novartis Vaccines and Diagnostics S.r.l. submitted to the European Medicines Agency on 16 August 2012 an application for a group of variations.

This application concerns the following medicinal product:

Medicinal product:	Common name:	Presentations:
Aflunov	prepandemic influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted)	See Annex A

The following variations were requested in the group:

Variations requested		**Type**
C.I.3.b	Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH	II
C.I.4	Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	II

The MAH proposed the update of sections 4.3, 4.4 to include barium sulphate among the trace residues and the update of section 4.8 to amend the duration of AEs in the post-marketing data as requested in the PSUR 2 review. In addition the MAH performed a cumulative review on cases of trombocytopenia and amended section 4.8 of the SmPC accordingly. The Package Leaflet was proposed to be updated accordingly.

The requested group of variations proposed amendments to the SmPC and Package Leaflet.

Rapporteur: Daniela Melchiorri

1.2. Steps taken for the assessment

Submission date:	16 August 2012
Start of procedure:	16 September 2012
Rapporteur's preliminary assessment report circulated on:	21 October 2012
Rapporteur's updated assessment report circulated on:	6 November 2012
CHMP opinion:	15 November 2012

2. Scientific discussion

2.1. Introduction

The prepandemic vaccine AFLUNOV has been approved for the active immunisation against H5N1 subtype of Influenza A virus in adults and elderly (18 years of age and older), outside of the context of a mock-up core dossier, that is, for prophylaxis before the pandemic is declared. This indication is based on immunogenicity data from healthy subjects following administration of two doses of the vaccine containing A/Vietnam/1194/2004 (H5N1)-like strain.

This vaccine was developed to protect against a (closely matched) potential influenza pandemic viral strain via early vaccination at the start of a pandemic or during pre-pandemic stages (e.g. to reduce mortality against a pandemic strain in those countries where infections are occurring). It may also help reducing the chance of the emergence of a reassortant pandemic strain by vaccinating those (e.g., veterinarians, poultry workers, operators involved in the manufacturing of vaccines with pandemic-like strains, laboratory workers) at high risk of infection from both avian and human viruses.

The pre-pandemic vaccine AFLUNOV is identical to the H5N1 pandemic mock-up vaccine, previously identified as Focetria, already approved in May 2007 for pandemic use. Currently the name Focetria identifies the actual H1N1 pandemic vaccine and the name Foclivia has been attributed to the H5N1 mock-up vaccine. With the exception of antigen composition and dose, AFLUNOV has as similar construct to the MRP authorized inter-pandemic seasonal vaccine Fluad. Both vaccines are egg-derived, surface antigen, inactivated, adjuvanted with MF59C.1 (MF59), and are produced following the same manufacturing process.

The variation discussed in this assessment report is a grouping of two type II variations. Three changes are proposed affecting SmPC sections 4.3, 4.4 and 4.8, as detailed below. Changes 1 and 2 were requested by the CHMP during its April 2012 meeting following the assessment of PSUR n. 2 (PSU011, covering period 29 May 2011 - 29 Nov 2011) for Aflunov. The third change was proposed by the MAH following a cumulative review performed at its own initiative.

1. SmPC sections 4.3 “Contraindications” and 4.4 “Special warnings and precautions for use” have been updated with the addition of barium sulphate to the list of substances whose traces or constituents can cause anaphylactoid and/or hypersensitivity reactions. The inclusion of barium sulphate among the manufacturing trace residues already listed in these sections is based on scientific literature reporting cases of anaphylactoid or hypersensitivity reactions following the administration of barium radiographic contrast formulation.

2. SmPC section 4.8 “Undesirable effects, adverse reactions from clinical trials in adults (18 years old and above)” has been updated concerning the text “These side effects usually disappear within 1-2 days without treatment”. The proposed text will state: “The majority of these side effects usually disappear within 1-2 days without treatment”. The inclusion of “The majority of” is based on the fact that some rare adverse reactions may not resolve within the indicated timeframe.

3. In addition, section 4.8 “Undesirable effects, post-marketing surveillance” has been updated concerning the text around “Transient thrombocytopenia”. The proposed text will state: “Thrombocytopenia (in some cases reversible platelet counts less than 5000 mm3)”. The removal of “transient” is based on the results of a cumulative review performed by the MAH of all thrombocytopenia confirmed cases in temporal association with the administration of an International Non-proprietary Name seasonal influenza vaccine.

2.2. Clinical Efficacy aspects

2.2.1. Analysis of data submitted

Barium Sulphate

Barium sulphate may be used during Aflunov manufacturing process to improve antigen purity and yield. Levels of residual contaminants, including barium, are controlled at the monobulk pooled harvest stage. When barium sulphate is used during manufacture, the presence of residuals is measured using Atomic Adsorption. The release specification for barium in the monobulk pooled harvest is ≤ 1 μg/mL.

Barium sulphate is also used in the field of radiography as a contrast agent. Cases of anaphylactoid or hypersensitivity reactions after the administration of barium contrast formulations have been reported in some individuals (Seymour et al, Anaphylactic shock during a routine upper gastrointestinal series, AJR 1997; Feczko et al, Fatal hypersensitivity reaction during a barium enema, *AJR* 1989; Janower, Hypersensitivity reactions after barium studies of the upper and lower gastrointestinal tract, *Radiology* 1986).

Thrombocytopenia

Primary Immune Thrombocytopenia Purpura (ITP) is an autoimmune disorder characterized by isolated thrombocytopenia in the absence of other causes or disorders that may be associated with thrombocytopenia. The main clinical problem of primary ITP is an increased risk of bleeding, although bleeding symptoms may not always be present. Several studies on the association between vaccines and ITP are available in the scientific literature. There is no strong evidence to link influenza vaccines use to ITP development. However, following the identification of an event of severe thrombocytopenia (platelet count <5,000/mm^3) in temporal association with an International Non-proprietary Name seasonal influenza vaccine, the MAH undertook a cumulative review of all cases of thrombocytopenia in temporal association with seasonal influenza vaccines. An overview of this review is provided below.

Methodology for the cumulative review of the cases of thrombocytopenia associated with the MAH' seasonal influenza vaccines

The safety database Argus was searched for spontaneous and clinical study cases of all the MAH seasonal influenza vaccines (Agrippal, Fluvirin, Begrivac, Fluad and Optaflu) using the Standard MedDRA Query (SMQ) search "HLT of Thrombocytopenia, PT of Platelet count decreased and Platelet destruction increased". All the spontaneous and clinical study cases were retrieved from the vaccines first launch through 6th February 2011. Only Novartis Vaccines and Diagnostics-confirmed cases were discussed in this cumulative review. The resulting reports were individually reviewed and analysed.

The Brighton Collaboration (BC) Working Group criteria were used to adjudicate all cases of thrombocytopenia. The definition of thrombocytopenia as an adverse event following vaccination proposed by this working group is summarized below:

Level 1 of diagnostic certainty (confirmed thrombocytopenia):

- Platelets count <150x10^9/L;
- Confirmed by blood smear examination or the presence of clinical signs and symptoms of spontaneous bleeding.

Level 2 of diagnostic certainty (unconfirmed thrombocytopenia):

- Platelets count <150x10^9/L.

Level 3 of diagnostic certainty:

- Not applicable.

All cases were further categorized based on severity of disease and causality as follows:

- Severity: Platelets level <50x10^9/L; Platelets level <25x10^9/L; Platelets level <10x10^9/L; Platelets level <5x10^9/L;
- Causality: Confounded due to presence of risk factors for thrombocytopenia, history of thrombocytopenia or other haematological disorders and concomitant medications known to induce thrombocytopenia.

In the literature, different times to onset have been used to analyse adverse reactions in relation with vaccination. The average lifespan of a platelet is normally 5 to 9 days. The MAH thus assumed a biological risk window of 4 weeks for a vaccine-induced thrombocytopenia. Therefore, cases occurring after 4 weeks post-vaccination were considered unrelated to the vaccine.

2.2.2. Results and discussion

Barium Sulphate

Based on the reports identified in the scientific literature related to the radiography field, it is assumed that hypersensitivity risks could be linked also to the barium residues potentially retained in the vaccine. Therefore the MAH proposes to include “barium sulphate” among the manufacturing trace residues listed in the current text of sections 4.3 “Contraindications” and 4.4 “Special warnings and precautions for use” of the SmPC, in order to alert health care providers.

Thrombocytopenia

A total of 100 individual cases of thrombocytopenia reported after the administration of seasonal vaccines were retrieved using the search criteria mentioned in section 2.2.1. Of these 100 cases, 40 did not have manufacturer information and the remaining 60 cases were reported with confirmed manufacturer. Of these 60 cases, 2 were duplicate reports hence the actual number of cases was 58. Of these 58 cases, 33 involved females and 25 involved males. The majority of the cases (31/58) occurred in the elderly >65 years of age, followed by adults 18 to 65 years of age (18/58), adolescents 10 to 17 years of age and children 2 to 9 years of age (2/58 each group). No cases were reported in infants <2 years of age.

Of the 58 cases of thrombocytopenia, 36 cases had platelet count <50,000/mm^3 after vaccination (this includes one case with life-threatening condition but no laboratory data reported) and 11 cases had platelet count ≥ 50,000/mm^3. For 11 cases platelet count was not provided. It is notable that the majority of the cases with a platelet level <50,000/mm^3 fall in the most severe sub-group of <5,000/mm^3. This is not unexpected given the fact that asymptomatic thrombocytopenia is detected only during routine blood examinations, while lower platelet levels are more likely to be associated with bleeding and promptly reported. Corrective treatment was necessary in many cases and the majority of them required more than one corrective treatment to recover from the thrombocytopenia. The large majority of cases describe petechiae or hematoma in limbs/trunk, followed by ear/nose/mouth bleeding. There were no cases of major bleeding (e.g. cerebral bleeding) possibly associated with the vaccine. There were 2 fatalities, both cases not related to the vaccine. Narratives of these 2 fatal cases, along with the narratives all other cases of special interests, are provided in the dossier.

Of the 58 cases, 33 were adjudicated as severity level 1. Of these, 30 occurred within the biologically plausible window as outlined in section 2.2.1. Of these 30 cases, 15 involved Begrivac, 8 Agrippal, 4 Fluvirin, and 3 Fluad.

Reporting rates of thrombocytopenia were generally very low. Considering cumulative doses distributed worldwide, approximately 140 million doses of Begrivac were distributed as compared with 112 million doses of Agrippal, 57 million doses of Fluad, and 408 million doses of Fluvirin. This accounts for a reporting frequency of thrombocytopenia cases of 0.02/100,000 doses for Begrivac, 0.009/100,000 doses for Agrippal, 0.018/100,000 doses for Fluad, and 0.002/100,000 for Fluvirin. Of note, these results may underestimate the actual incidence mainly because not all doses distributed may have been administered and because of the well-known underreporting of spontaneous reports. In addition, epidemiologic studies on ITP clearly suffer from a lack of a uniform definition of the disease that would allow for reasonable comparisons. In conclusion, although the cumulative review was conducted on the post-marketing data from seasonal vaccines, the MAH proposed a conservative approach to apply the SmPC variation also to the listed event "transient thrombocytopenia" in the post-marketing safety section of the SmPC for pandemic vaccines. Specifically, the proposed removal of the word "transient" is based on the fact that the results of the cumulative review do not confirm the self-limiting nature of thrombocytopenia in the majority of the cases reported for seasonal vaccines.

2.3. Clinical Safety aspects

Adverse reactions duration in adults (18 years old and older)

The incidence of adverse reactions reported in adults (18 ≥ 60 years of age) and elderly (≥ 61 years of age) in the Aflunov SmPC is based on data from 7 clinical trials involving over 4300 subjects receiving Aflunov. All adverse reactions are listed under section 4.8 "Adverse reactions from clinical trials in adults (18 years old and above)" of the Aflunov SmPC. With regards to the duration of these adverse reactions, the current text states "These side effects usually disappear within 1-2 days without treatment". Based on the vaccine safety data, the majority of reported adverse reactions disappear within 1 or 2 days without treatment. However, some severe and rare adverse reactions, such as anaphylaxis or convulsion, may not resolve within 1 or 2 days without treatment. Therefore, the MAH proposes to reflect this important point in section 4.8 of the SmPC, as outlined below.

2.4. Changes to the Product Information

The MAH proposed the following changes to the Product Information (PI), to which the CHMP agreed (new text underlined, deleted text strikethrough):

- SmPC **section 4.3** Contraindications:

  History of an anaphylactic (i.e. life-threatening) reaction to any of the constituents or trace residues (egg and chicken proteins, ovalbumin, kanamycin and neomycin sulphate, barium sulphate, formaldehyde and cetyltrimethylammonium bromide (CTAB)) of this vaccine.

- SmPC **section 4.4** Special warnings and precautions for use:

  Caution is needed when administrating this vaccine to persons with a known hypersensitivity (other than anaphylactic reaction) to the active substance, to any of the excipients and to residues (eggs and chicken proteins, ovalbumin, kanamycin and neomycin sulphate, barium sulphate, formaldehyde and cetyltrimethylammonium bromide (CTAB)).

- SmPC **section 4.8** Undesirable effects - Adverse reactions from clinical trials in adults (18 years old and above):

The majority of these side effects usually disappear within 1-2 days without treatment.

- SmPC **section 4.8** Undesirable effects - Post-marketing surveillance - Blood and lymphatic system disorders:

  ~~Transient~~ tThrombocytopenia (in some cases reversible platelet counts less than 5000 per mm^3).

3. Overall conclusion and impact on the benefit/risk balance

Following the assessment of the PSUR 2, the CHMP during its meeting in April 2012 recommended the update of sections 4.3 or 4.4 of the SmPC based on re-assessment of scientific literature on hypersensitivity cases linked to barium sulphate in the field of radiography. These cases prompted the listing of barium sulphate among the other potential trace residues in the vaccine, which can give rise to hypersensitivity reactions of varying degrees of severity. Because this element can be used in the manufacturing process, traces may be retained in the final formulation. In addition the update of section 4.8 of the SmPC was also recommended by the CHMP, concerning the duration of adverse events listed in the post-marketing surveillance data section: not all these adverse events will disappear in one or two days without any treatment as originally stated in the SmPC, but only the majority of them will.

The MAH submitted a group of two type II variations: one to implement the recommendation of the CHMP as detailed above and another one to implement changes in section 4.8 of the SmPC concerning the text around transient thrombocytopenia in association with the use of seasonal vaccines. Following a cumulative review of cases of severe thrombocytopenia associated with the use of seasonal vaccines, the MAH proposed the deletion of the word transient and the inclusion of the information that some cases with platelets counts <5,000mm^3 were observed. Due to the nature of the post-marketing data a clear cut frequency of event for thrombocytopenia could not be defined, however the inclusion of this information in the SmPC of Aflunov is agreed as a conservative approach.

The Package leaflet is updated accordingly.

Overall these variations do not affect the benefit/risk balance of the vaccine, which remains positive.

4. Recommendations

Based on the review of the submitted data, the CHMP considers the following group of variations acceptable and therefore recommends the variations to the terms of the Marketing Authorisation, concerning the following changes:

Variation(s) accepted		**Type**
C.I.3.b	Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH	II
C.I.4	Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	II

Update of sections 4.3 and 4.4 of the SmPC in order to add a contraindication and a warning for cases of known hypersensitivity to barium sulphate, which has been added to the list of trace residues. In addition, section 4.8 of the SmPC was updated concerning the duration of adverse events based on

post-marketing surveillance data and concerning cases of thrombocytopenia based on a cumulative review data. The Package Leaflet is updated accordingly.

The requested group of variations procedure proposed amendments to the Summary of Product Characteristics and Package Leaflet.