European Medicines Agency

London, 19 Novmeber 2009
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CHMP VARIATION ASSESSMENT REPORT

Invented name/Name: Pandemrix
International non-proprietary name/Common name: pandemic influenza vaccine (H1N1) (split virion, inactivated, adjuvanted) A/California/7/2009 (H1N1)v like strain (X-179a)

TYPE II VARIATION: EMEA/H/C/000832/II/0026

Indication summary (as last approved):	prophylaxis of influenza
Marketing Authorisation Holder:	GlaxoSmithKline Biologicals S.A.

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

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I. SCIENTIFIC DISCUSSION

1.1. Introduction

Pandemrix was granted Marketing Authorisation in the EU in May 2008, with use being restricted to subjects aged 18-60 years in section 4.2 of the summary of product characteristics (SPC) due to lack of data outside of this age range. The granting of the initial Marketing Authorisation was based on a mock-up vaccine derived from A/VietNam/1194/2004 (H5N1) like strain (NIBRG-14).

Following the declaration of the pandemic phase 6 by the World Health Organisation (WHO), the MAH applied for a strain change to include the pandemic H1N1v strain.

The currently approved vaccine contains split influenza virus with a haemagglutinin content equivalent to 3.75 micrograms derived from A/California/7/2009 (H1N1)v-like strain (X-179A). The virus is propagated in eggs and the approved vaccine is manufactured in Dresden.

The vaccine also contains the marketing authorisation holder's (MAH's) proprietary adjuvant AS03, which is composed of squalene, DL-alpha-tocopherol and polysorbate 80.

The MAH applied to update section 4.8 and 5.1 of the Summary of Product Characteristics (SPC) for Pandemrix H1N1 to reflect newly available results from post authorisation spontaneous reporting following initiation of the vaccination campaigns in Sweden and the UK in view of allergic and anaphylactic reactions.

1.2 Clinical aspects

At the time of submission, the only information available other than adverse event data submitted in the UK is a summary of the safety experience produced by Sweden. This was posted on the Swedish MPA website on 29 October.

Given that the current product information for Pandemrix reflects only the safety experience from H5N1 or H1N1 clinical trials, as well as post-marketing experience with seasonal influenza vaccines, this assessment report considers an amendment to the product information to include Swedish and UK data on suspected ADRs.

Data from Sweden

The latest information available from Sweden indicates that up to 2 million doses have now been administered. This includes use in pregnant women and children.

In total, about 600 ADR reports have been received by the Swedish MPA from Health Care Professionals and almost 900 reports from consumers. The general safety experience in Sweden broadly reflects the known ADRs identified in the clinical trials, however, serious allergic reactions have also now been reported.

According to MPA, the majority of the adverse events are expected and known reactions such as soreness, redness and pain at the injection site and in the arm, and flu-like symptoms such as fever, shivering, fatigue, moderate/severe headaches, body aches and malaise. Such events are established adverse effects of the mock-up vaccines (and many vaccines) and as there is presently no suggestion of a change in frequency or severity of such events. As these are already listed in the Pandemrix SPC, the cases reported so far do not warrant any regulatory action.

Eight events with a fatal outcome have so far been reported in Sweden. These patients had previously known chronic diseases such as cardiovascular disease, diabetes, renal failure, dystrophic muscle disease and senile dementia. All patients were on chronic medical treatment. At least three of the patients were aged >74 years. A Post mortem report is available for four of the cases and in all these cases a relation between the vaccination and the death is considered unlikely. For the other cases there

is insufficient information and autopsy protocols are lacking which limits the assessment. According to the MPA, there is currently no basis to support a causal association between vaccination and the deaths.

The MPA has also received almost 900 consumer reports. About 90% of reports describe non-severe, expected and known reactions. Despite the fact that many of these adverse effects are known and listed, some patients have apparently reported that the reactions to Pandemrix vaccine differ from their experience with previous seasonal flu vaccinations, such as more pronounced pain in the injection arm and stronger flu-like symptoms. At present, this information does not warrant any regulatory action.

The key issue emerging from the Swedish data so far is the nature of reported allergic reactions. The following table summarises the cases reported:

Table 1: Allergic reactions

Reaction	Known allergy (no of patients)	Serious reactions	Non serious reactions	Total no of reported reactions
Allergic reaction	12	4	14	18
Anaphylactic reaction	6	11	1	12
Anaphylactic shock	2	2		2
Angioedema	1	5	8	13
Oedema in mouth and throat	1	1	9	10
Urticaria	1	1	20	21
Exanthema			12	12
Flush	2	1	8	9
Itching	4	1	16	17
Asthma - worsened	1	1	4	5
Dyspnoea	2	4	14	18
Total	**32**	**31**	**106**	**137**

According to the MPA, several of the patients with a severe hypersensitivity reaction had known allergies to pollen, grass, medicines, certain foods such as eggs, nuts, fruit, peanuts, fish, etc. In most of the cases deemed serious, the patients needed treatment with antihistamines, adrenaline and cortisone and supervision in hospital. In all cases, the hypersensitivity reactions have resolved rapidly and completely. Two cases of anaphylactic shock have been reported. In one case the patient had a known egg allergy; the other patient was allergic to several foods, including nuts, but not to eggs. The reports on allergic reactions shows that not only allergy to substances in the vaccine such as egg gives rise to reactions, but also other forms of allergic tendency seems to be able to contribute to an allergic reaction.

Assessment of the individual case narratives suggests that whilst some of the cases of reported anaphylaxis may include the symptoms suggestive of a serious anaphylactic-type reaction (i.e. in accordance with the Brighton Collaboration definition), at least half of these cases could also be either a mild allergic reaction or possible a psychogenic reaction. However, it is known that any vaccine can cause anaphylaxis and, despite no cases being observed in the Pandemrix clinical trials, it is entirely plausible that Pandemrix may rarely cause anaphylaxis and angioedema. In the absence of any other obvious trigger, such events occurring in very close temporal association with vaccination are most likely to be causally associated with vaccination. Indeed, only a single reported case with reasonable diagnostic certainty and possible causality would warrant inclusion in the SPC.

Fourteen possible case reports of anaphylaxis in the context of around 2 million doses administered would be in line with the broadly accepted frequency estimates of vaccine-induced anaphylaxis (i.e. between 1 and 10 cases per million individuals immunised), albeit at the upper end of this estimated range Although this is only an estimated reporting rate, and not a robust incidence rate, there is still no apparent excess risk of anaphylaxis or allergic reactions at present, particularly as some of the reported cases may actually be only mild allergic reactions or possible psychogenic reactions. Given the high profile nature of swine flu immunisation campaigns at present, under-reporting of suspected ADRs may well be less at present than with most well-established vaccine programmes. However, it must still be acknowledged that under-reporting is a factor and therefore reporting rates must be considered with this in mind. Reporting rates of allergic reactions must be kept under close review as exposure data become available in other countries.

Anaphylaxis is the medical term reported in these case reports and, although such cases could possibly be anaphylactoid and not truly allergic in nature, there is insufficient laboratory or clinical details to distinguish anaphylaxis from an anaphylactoid reaction. The SPC term 'Anaphylaxis' adequately covers the clinical manifestation of such reactions.

Although the Swedish report also states that some of the patients who experienced anaphylaxis had had a known allergy to certain foods or medicines, there is no further information to assess any specific sensitizing risk factor. Section 4.3 of the SPC currently lists as contraindications "History of an anaphylactic (i.e. life-threatening) reaction to any of the constituents or trace residues (egg and chicken protein, ovalbumin, formaldehyde, gentamicin sulphate and sodium deoxycholate)". Section 4.4 also states that "Caution is needed when administering this vaccine to persons with a known hypersensitivity (other than anaphylactic reaction) to the active substance, to any of the excipients, to thiomersal and to residues (egg and chicken protein, ovalbumin, formaldehyde, gentamicin sulphate and sodium deoxycholate)" and "As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of a rare anaphylactic event following the administration of the vaccine". There is currently no evidence to support any strengthening or amendment to sections 4.3 and 4.4 in this respect.

Data from UK

At present the number of doses administered in the UK (as well as other EU Member States) is not available. In the UK, we have received 645 reports of suspected ADRs as of 16 November.

The most frequently reported suspected adverse reactions have been injection site reactions (e.g. pain, swelling, redness, bruising) or general minor adverse effects already listed based on the experience in the clinical trials (mainly nausea, vomiting, muscle pain, fever, fatigue, headache, lymphadenopathy). Two cases of anaphylaxis have been reported, although the available clinical details do not suggest that these were truly anaphylaxis. Several case reports of generalised skin reactions have also been reported. The SPC currently states that 'generalised skin reactions' have been reported with seasonal flu vaccines. Other than moving 'generalised skin reactions' to the Pandemrix H1N1 section of the SPC, the UK ADR data, at present, do not warrant any other amendments to the SPC.

Conclusions and Benefit / Risk Assessment

The post-marketing experience was considered to be in line with the known, and listed, adverse effects of the mock-up vaccines. However, the emerging data on serious allergic reactions in association with Pandemrix warranted amendments to the SPC and PIL. .As the PI has been updated the balance of risks and benefits is not affected by these data at present.

1.3 Changes to the Product Information

The detailed changes can be found in the final approved highlighted SPC/Annex II/ /PL attached to this report. Further to the assessment and the scientific discussions held at the CHMP, the following changes to the Product Information were requested and subsequently implemented by the MAH.

SPC section 4.8 - Undesirable effects

The first paragraph in the sub-section on Pandemrix H1N1v was updated to reflect that in addition to the adverse reactions reported in the clinical trials (both H5N1 and H1N1), the reactions in this section have been reported during post-marketing experience with Pandemrix H1N1v.

In addition the adverse events “generalised skin reactions” and “allergic reactions” have been moved to this section from the section on interpandemic trivalent vaccines, in line with the post-marketing experience data.