



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

## Assessment report

### Pandemrix

Influenza vaccine (H1N1) (split virion, inactivated, adjuvanted) A/California/7/2009 (H1N1)v like strain (x-179a)

**Procedure No.:** EMEA/H/C/000832/A20/0045

### Note

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

Medicinal product no longer authorised



## 1. Scientific discussion

Pandemrix is a (H1N1)v split virion, inactivated, adjuvanted influenza vaccine, authorised for prophylaxis of influenza caused by A (H1N1)v 2009 virus. During the swine flu pandemic, Pandemrix was the predominant swine flu vaccine used within the EU, with more than 30 million doses administered.

Following initial spontaneous case reports of narcolepsy in temporal association with Pandemrix vaccine, mainly in Finland and Sweden, including case clusters from single reporters, the EC initiated a procedure under Article 20 of Regulation (EC) No 726/2004 and requested the CHMP to assess this concern and its impact on the benefit/risk balance for Pandemrix. Narcolepsy is a chronic neurological inability to regulate sleep-wake cycles normally. Narcolepsy typically consists of a 'tetrad' of symptoms; excessive daytime sleepiness (EDS), cataplexy, sleep paralysis, and hypnagogic/hypnapompic hallucinations. However, most patients do not present with all four symptoms. Additional features may include automatic behaviours and fragmented or disrupted night time sleep. Its precise cause is unknown, but it is generally considered to be triggered by a combination of genetic and environmental factors, including infections.

Several data sources informed the opinion of the Committee, including all data submitted by the MAH. Cases of narcolepsy reported through spontaneous reports, including 'observed versus expected' (O/E) analysis of such reports from several member states were available. Results from epidemiological cohort studies in Finland and Sweden, results from a case inventory study in Sweden and preliminary results from the VAESCO consortium were deemed relevant for this review. The outcome of the expert meeting held was also considered.

### 1.1. Clinical aspects

#### 1.1.1. Spontaneous reports

Analysis of spontaneous case reports in Finland and Sweden indicated a signal of excess reports of narcolepsy following vaccination with Pandemrix, relative to the age-specific background incidence (i.e. O/E analysis). The signal was apparent only amongst children and adolescents aged 4-19 years, with no clear excess reporting in adults. Pandemrix was the only H1N1 vaccine used in these two countries during the pandemic.

Passive surveillance indicates excess reporting of narcolepsy relative to expected background incidence in France, Germany, Ireland, Norway and the United Kingdom (UK), and details are presented below. The increased reporting was evident only after awareness of the signal in Finland and Sweden and some analysis include cases for which diagnosis has not been confirmed (see below for specific available O/E analysis).

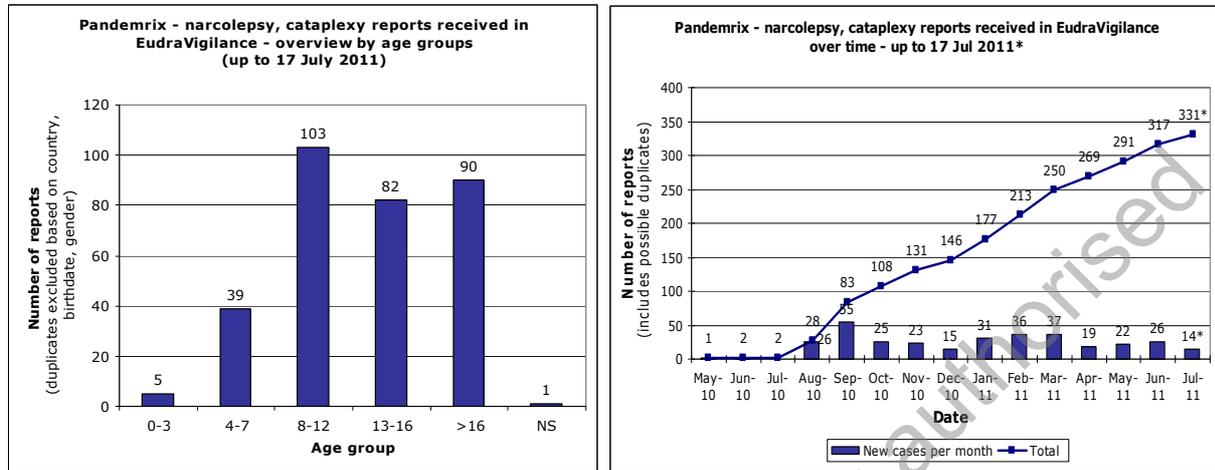
There was no indication of any batch-specific signal based on analysis of spontaneous case reports across Europe. Reports of narcolepsy have been associated with a wide range of vaccine batches. Likewise, an overview of the reporting rates of narcolepsy cases for Pandemrix lots produced with different triton-x concentrations<sup>1</sup> (used in manufacturing to prevent aggregation and precipitation of

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<sup>1</sup> Variation II.18, from October 2009, introduced these changes in the manufacturing process of the H1N1 antigen component.

biomolecules, to disintegrate the virus particles in split vaccine and to guarantee the homogeneity during production and utilisation) did not suggest a signal.

A cumulative presentation of suspected cases of narcolepsy passively reported across the EU (up to 17 July 2011) is presented below.



By 17 July 2011, a total of 320 suspected cases of narcolepsy/cataplexy had been received in EudraVigilance, originating from 10 countries. Most of these cases were in patients aged less than 16 years (approximately 72%). Please note these figures can include duplicates.

The evaluation of case reports of narcolepsy has inherent limitations, does not allow causality to be assessed and may only be considered hypothesis generating. Formal epidemiological studies are required and therefore it is considered that cumulative assessment of additional case reports will add little value to the risk assessment.

Nevertheless, a brief summary of available safety surveillance (O/E) analysis is described below. Note that the figures do not account for diagnostic uncertainty and underreporting, different processes were used to calculate the background incidence rate and the risk period varied between analyses. These figures are thus informative. The majority of reports were notified after media attention (see also the figure above: Pandemrix – narcolepsy, cataplexy reports received in EudraVigilance over time).

### France

In communication from 4 April 2011, a total of 25 cases (10 female and 15 male) of narcolepsy (of which 20 with cataplexy) had been reported in France for Pandemrix (23 cases out of 4,100,000 vaccinated people) and another vaccine (2 cases out of 1,600,000 vaccinated people). Of the 25 cases, 14 were reported in people 16 years of age or above; and 11 in adolescents 8 to 15 years old.

The selected at-risk period was 150 days. Analyses were stratified by [0-9] years old, [10-15] years old, [16-45] years old, and ≥65 years old. For those aged 10 to 15 years of age, the number of observed cases exceeded the expected annual incidence: 9 observed cases of narcolepsy on a population of 670,000 adolescents vaccinated with Pandemrix versus 2.1 expected (i.e. an O/E ratio of 4.3).

### Germany

As of 7 July 2011 a total of 20 suspected cases of narcolepsy following H1N1v influenza vaccination were reported, 14 of which in children and adolescents <18 years of age. Of these 14 subjects 5 were males and 9 females. Two of the 14 subjects reported to have experienced excessive daytime

sleepiness prior to vaccination and were therefore excluded from further analysis. Two of the remaining 12 cases were classified as Brighton Collaboration (BC) level 1, three cases as BC level 2, two cases as level as BC level 3, three cases as level 4a, and two cases as level 4b.

The O/E analysis was calculated including cases meeting the criteria of the BC levels 1–3 (n=7). A total of 1.08 incident cases of narcolepsy was expected, and approximately 897,500 children and adolescents <18 years of age were vaccinated with Pandemrix (i.e. O/E ratio of 6.5).

### **Ireland**

As of 11 July 2011, a total of 13 reports (12 in adolescents/children) were received with clinical information consistent with a diagnosis of narcolepsy. Half of these reports were in children aged 12-13 years. Two thirds of the total reports in children/adolescents were in the age range 10-13 years. Eleven of the 13 cases were in females (10 children/adolescents and 1 adult).

Two thirds of the total reports in children/adolescents were in the age range 10-13 years. The O/E ratio with a 6 month risk period would be estimated as 2 for the age range 0-9 years (2 cases), 1.5 for the age range 10-19 years (9 cases) and 6.7 for the age range 50+ (the latter is based on a single report) based on the 6 month risk period. One case was outside the 6 month risk period.

### **Norway**

A total of 23 reports of narcolepsy were reported for Pandemrix in Norway by 15 July 2011, 19 of which concerning children and adolescents aged 4-19 years. Vaccinated children were stratified by [6months-2years], 80 173; [3-9years], 242 069; [10-19years], 276 246. The total number of vaccinated children in Norway was thus 598 488. The number of observed cases exceeded the expected incidence: 19 observed cases in a population of ~ 500 000 among children 4-19 years vaccinated with Pandemrix versus 5 expected (i.e. an O/E ratio of 3.8).

### **United Kingdom**

The UK O/E analysis did not show an overall excess reporting of narcolepsy across all age groups following vaccination with Pandemrix, with an observed 9 cases versus an expected 14 cases. However, an excess was observed within specific age bands and particularly within the 5-15 year old age band where a 9-fold excess was observed (4 cases observed, 0.43 expected). A non-significant excess was also observed for the 6months-4years age band but this is based on a single observed case. A risk period of three months was chosen. A diagnosis of narcolepsy has been confirmed for only one of these cases so far, and all were reported after the initial media attention in July/August 2010.

## **1.1.2. Epidemiological evidence**

Several data sources have now yielded results relevant to the potential association between vaccination with Pandemrix and narcolepsy. A summary of the results of these studies is presented below.

### **Retrospective cohort study in Finland**

A nation-wide immunisation campaign with Pandemrix was carried out in autumn 2009, with an average national coverage of approximately 50% of the population (approximately 2.7 millions). A cluster of cases of narcolepsy were reported during 2010. Comparison with historical, age-specific incidence rates suggested a greater than expected reporting rate, particularly in children and adolescents.

To investigate this issue a retrospective cohort analysis was performed by THL to assess the incidence of narcolepsy amongst 4 to 19 year olds in Finland who were vaccinated with Pandemrix compared to those who were unvaccinated. The preliminary results of the THL cohort study are summarised below.

Cases of narcolepsy diagnosed between 1 January 2009 and 31 December 2010 were identified using the Finnish National Hospital Discharge Register. As of 24 January 2011, the THL adverse drug reaction (ADR) register contained 57 reports of suspected narcolepsy following Pandemrix, 54 of which were in children and adolescents. The institute stated that the majority of the cases had a classic narcoleptic/cataplectic syndrome and most had been confirmed with sleep polygraphy and multiple sleep latency test (MSLT).

The expected incidence amongst 4 to 19 year olds, based on 5 to 16 cases from 2006 to 2009, was approximately 1 case/100,000 person years. The observed reporting rate amongst this immunised age group in 2010 was 8.1/100,000 person years (n=54).

Immunisation of 4 to 19 year olds occurred mainly during the tail of the pandemic peak in Finland, and was given via a schools-based programme. The study cohort included 915,854 subjects born between 1991 and 2005. During the study period, 646,449 (70.6%) subjects were vaccinated with Pandemrix and 269,405 (29.4%) were never vaccinated with Pandemrix. Vaccinated subjects contributed risk time in the unvaccinated group until the time point at which they were vaccinated.

The index date was the date of first health care visit with symptoms of narcolepsy. The average time from vaccination to the onset of excessive day time sleepiness or cataplexy was 52 days. The shortest time interval was on the same day, the longest time was 8 months. The distribution according to gender was 24 males and 33 females.

The main preliminary analysis, restricted to cases with first visit before the widespread public concern in Finland, found an increased relative risk of narcolepsy in the vaccinated group of 9.2 (95% CI: 4.5-21.4). These results were preliminary, as in some of the cases there was not sufficient information to make a robust estimation of the onset time. Sensitivity analyses using different index dates still showed statistically significant relative risks.

In 2010, there were 40 new diagnoses of narcolepsy in adults, a slightly lower number than in the previous years. Of these, 22 had been vaccinated. Vaccination coverage in this age group was 43%. The data did not suggest an increase in incidence of narcolepsy among those older than 19 years of age.

The Finnish retrospective cohort study was completed in May 2011. As of 4 July 2011, the result for relative risk ratio in the vaccinated group was of 12.7 (95% CI: 6.1-30.8). The index date was first contact from 01.01.2009 to 15.08.2010 (46 cases vaccinated versus 7 non-vaccinated).

### **Retrospective cohort study in Sweden**

A nation-wide vaccination program against pandemic influenza A/H1N1 using Pandemrix was carried out from mid-October 2009 to March 2010, with an average national coverage of approximately 60 percent. Starting during the summer 2010, an increasing number of spontaneous reports of narcolepsy were received in Sweden, especially in children/adolescents. The number of reported cases in the age 19 and younger exceeded the expected number.

To investigate this issue, a preliminary analysis of data from Stockholm, Sweden was performed in October 2010 by the Medical Products Agency (MPA) but did not yield a sufficient number of cases of narcolepsy for any firm conclusions. The preliminary results of the MPA cohort study using national hospital registry data from a larger study population comprising four counties (57% of the Swedish population) are summarised below.

The study population was defined as all individuals resident in four counties on 1 October 2009 (in total, 5.3 out of 9.3 millions, 57%). Exposure to Pandemrix was identified from regional vaccination registries. Individuals who received at least one dose of the vaccine were defined as exposed. In the cohort of vaccinated subjects the follow-up time was defined as exposed from the date of vaccination until the end of follow-up. Vaccinated subjects contributed exposure time in the unvaccinated cohort from 1 October to the date of vaccination.

Incident cases of narcolepsy were defined as individuals with a first record for a diagnosis of narcolepsy in county health care databases from 1 October 2009 in those non-vaccinated or after the first vaccination among those vaccinated.

Estimates of historical incidence were calculated based on national data of patients obtaining their first diagnosis of narcolepsy between 2005 and 2008 in an in-hospital setting or at an ambulatory care visit at specialist clinics.

A total of 38 cases of narcolepsy were identified amongst vaccinated individuals aged 19 years or less and a total of 6 cases in the non-vaccinated group. Of the 38 vaccinated cases, 20 had the diagnosis of narcolepsy after 1 August 2010, including 15 cases diagnosed after 1 September 2010.

The median onset of narcolepsy from the time of vaccination was 261 days with a range of 61 to 408 days. The distribution in males and females was similar.

The incidence of narcolepsy among vaccinated children aged 19 years or less was 4.06 cases per 100,000 person years, compared with an incidence of 0.97 cases per 100,000 person years among unvaccinated. These rates yield a relative risk of 4.19 (95% CI: 1.76-12.1) for vaccinated children/adolescents as compared with non-vaccinated which corresponds to an attributable risk of 3 cases per 100,000.

The incidence rate among adults was 1.16 per 100,000 person years for vaccinated and 0.96 per 100,000 person years for unvaccinated, corresponding to a relative risk of 1.21 (95% CI: 0.67-2.17). No apparent differences between the four counties, with respect to incidence rates or to relative risk estimates, were observed. However, the power of detecting such differences is limited.

The average historical incidence of narcolepsy between 2005 and 2008 was estimated at 1.04 per 100,000 (95% CI: 0.92-1.16) persons aged 20 years and older and 0.46 per 100,000 (95% CI: 0.32-0.60) in persons under 20 years of age. The historical incidence in adults is almost identical with the incidence among both vaccinated and unvaccinated during the study period. The historical incidence in children was about half of that observed for the unvaccinated during the study period, however this difference was not statistically significant ( $p=0.10$ ).

### **Case inventory study in Sweden**

On 30 June, the findings of a case inventory study investigating the association between Pandemrix and reports of narcolepsy in Sweden were made available.

The study was designed to investigate the incidence of narcolepsy with cataplexy in the entire Swedish population over time irrespective of vaccination status, i.e. during and after as compared with before the pandemic period. The study compared the incidence of narcolepsy with cataplexy in subjects vaccinated with Pandemrix with unvaccinated subjects during the pandemic period and thereafter, and describes and compares characteristics of exposed and non-exposed narcolepsy with cataplexy cases.

The study focused on children/adolescents, as there is no evidence to date of an increased risk for narcolepsy in adults.

Numbers and incidence rates of narcolepsy cases by gender and age groups were calculated during different time periods (by quarter over the whole study period and over time intervals defined in

relation to the pandemic i.e. pre-pandemic, pandemic/vaccination period and post pandemic period). Additionally an analysis was also performed for different time windows post-vaccination i.e. 3 months.

Cases of narcolepsy with cataplexy, defined by date of onset of first symptom were related to person-years of observation in vaccine exposed vs. unexposed children/adolescents, both overall and in defined age groups ( $\leq 9$ , 10-14, 15-19 years).

Patient clinical characteristics were compared by vaccination status for age, gender, first registered symptom, number of symptoms during the first month, proportions with a positive Multiple Sleep Latency Test (MSLT), levels of hypocretin, proportions with 2 specific human leukocyte antigen (HLA) haplotypes, normal Magnetic Resonance Tomography (MRT) or Computerised Tomography (CT) and with abnormal weight gain.

Data were compiled for the three defined periods: pre-pandemic period (January-September 2009) incidence rate 0.31/100,000 person years; pandemic-vaccination period (October 2009-March 2010) incidence rate of 5.78; post-pandemic-vaccination period (April- December 2010) incidence of 0.79.

Incidence rates calculated over the whole study period (1 January 2009 –31 December 2010) were also seen to vary with the latitude of the region with the highest rates observed in the southern regions (2.14-2.99/100,000 person-years) compared with the middle regions (0.99-1.88/100,000 person-years) and the northern region (0.25/100,000 person-years).

A total of 81 cases of narcolepsy with cataplexy were identified for the whole study period of which 69 had been vaccinated before the onset of the first symptom, compared with 7 unvaccinated cases occurring during the pandemic period. The incidence rate in those vaccinated was approximately seven-fold higher than in the non-vaccinated subjects (4.2 vs. 0.64 per 100,000 person-years, RR = 6.6 [95% CI: 3.1-14.5]) and an absolute risk of 3.6 additional cases [95% CI 2.5-4.7] per 100,000 vaccinated subjects.

Of the 69 cases, 53 cases (76.8%) had onset of symptom within three months after the date of vaccination and 16 (23.2%) later than three months. The overall incidence during the first three months of follow-up was 14.1/100,000 (compared with unvaccinated cohort: RR = 22.0 [95% CI 10.0-43.4]) and in the later time window 1.28/100,000 person-years (compared with unvaccinated cohort: RR = 2.0 [95% CI: 0.8-4.9]).

There were no significant differences between vaccinated and non-vaccinated cases with regard to gender and age distributions. However, vaccinated cases seemed to be different from un-vaccinated cases regarding some characteristics described in the medical records. Vaccinated cases appeared more likely than non-vaccinated cases to present with cataplexy during the month of onset, (43% versus 8%), and with two or more simultaneous symptoms, 46 % versus 17%. Regarding laboratory results, no differences could be identified but results are uncertain due to limited availability of data.

### **Retrospective cohort study in Europe - VAESCO**

The aim of the VAESCO narcolepsy study<sup>2</sup> is to assist in providing more information on the association between vaccinations, infections and narcolepsy and the potential public health impact. The study is being conducted in eight European countries (Denmark, Finland, France, Italy, The Netherlands, Norway, Sweden, and the United Kingdom). The specific objectives were to assess:

- 1) The background rate of narcolepsy (2000 to 2010)

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<sup>2</sup> The study was intended to be conducted in 2 phases. Phase 1 was to yield rapid results and is based on chart review. Phase 2 (not initiated yet) would involve sampling of oral mucosal cells or blood for HLA typing of cases and controls and potential genetic studies.

2) A potential change in narcolepsy rates after April 2009 (i.e., beginning of H1N1 Pandemic in Europe) and October 2009 (i.e., beginning of immunisations in Europe), respectively.

3) The potential association between risk factors including influenza, infections vaccinations and narcolepsy in an analytical study.

A summary of the preliminary analysis of data<sup>3</sup> is now available and presented below. The study is still ongoing.

The background rates of narcolepsy were determined through a dynamic retrospective cohort study. Risk factors for narcolepsy are studied through a retrospective case-control study.

#### Population-level background incidence

The data indicated that incidence rates are age dependent with the highest peak observed between 15-35 years of age. A seasonality with annual winter peak was observed.

In Finland, an increase in the incidence rate of narcolepsy diagnoses in children/adolescents 5-19 years of age (but not in adults/elderly) was observed. Sweden did not yet provide data for the pandemic period and therefore changes could not be assessed. Norway could not exclude prevalent cases and could not use the distributed data model software (Jerboa). The data for Norway was therefore not pooled, but the analysis in the children /adolescents 5-19 years of age showed that there was no increase in narcolepsy diagnoses in 2010.

In The Netherlands the incidence rate was low because the database was small and many cases were considered invalid after validation. No increase in incidence in the H1N1 vaccine targeted age groups (> 60, < 5 years and risk groups) was seen after the vaccination campaign started.

In Italy and UK, no increase in incidence rates was observed in the targeted age groups. In Denmark an increase in the incidence of narcolepsy was observed after August 2010 pointing to increased awareness. The increase occurred only in the age group that was not targeted for vaccination.

Based on the available background rates, the increased incidence of narcolepsy diagnoses after the start of the H1N1 vaccination campaign could be observed only in Finland in children/adolescents 5-19 years of age.

#### Case control study

A nation wide case recruitment is being undertaken for Finland, Sweden, the Netherlands and Denmark (for the UK and IT, a subset of the population was considered). So far, 53 cases of narcolepsy from signalling countries<sup>4</sup> were included in the analysis (41 in children and adolescents). From non-signalling countries, 44 cases were available (17 children and adolescents).

The primary analysis in all ages resulted in overall matched estimates for the association between H1N1 vaccination exposure and narcolepsy of 5.61 for Finland (95%CI: 1.24-25.4) and 2.03 for Sweden (0.20-20.3). For the Netherlands the estimate was 3.2 (0.3-39). Estimates could not be calculated for Denmark, Italy and the UK separately as there was no exposure in cases.

Pooling of data from the non-signalling countries yielded an overall matched odds ratio of 1.84 (95%CI: 0.21-15.9).

When results were stratified by age, the estimation was difficult since many case control pairs were concordant, especially in Sweden which has very small numbers of controls. Matched analyses showed high non-significant and unstable odds ratios ((OR=32.7 (0.5-2150) in Finland and OR= 38 (0.01-

<sup>3</sup> The interim report does not yet include data from France and Denmark.

<sup>4</sup> Signalling countries are Finland and Sweden, where the signal was first identified.

21,000) in Sweden) in both countries. To improve the estimation, a non-matched analysis was performed with adjustment for the matching factors (age/sex/month) which yielded the following estimates: In Finland: OR=6.34 (95%CI: 1.29-31.2); for Sweden: OR=4.38 (95%CI: 0.26-72). In both countries no association was found for adults: Sweden: OR=0.44 (95%CI: 0.03-5.97), Finland: 0.94 (0.16-5.62).

The association between pandemic H1N1 vaccination and narcolepsy was confirmed in Finland. The estimated risk ratio was lower than the risk ratio of the generating cohort study. This could be due to adjustment for age, sex and calendar time in the case control study, and the slightly different age cut (5-18 years of age) and censoring (period up to July, instead of August). The association was not significant in Sweden, but only partial data has been collected so far. No association between pandemic H1N1 vaccination and narcolepsy was observed in adults.

The number of exposed cases was very limited outside of the signalling countries, therefore no estimate could be calculated for children /adolescents.

Complete data collection on cases and controls is not yet achieved. Once these data are available, VAESCO will conduct fully adjusted analysis including infections and other vaccinations. The study will also explore how media attention may have affected the results.

### **1.1.3. Other initiatives**

#### **Expert meeting**

An expert meeting was held on 12 July 2011 in order to inform the CHMP opinion to discuss scientific evidence base for the safety signal, and need for further data. The meeting addressed 6 broad questions relating to the strength of epidemiological evidence, potential co-contributory factors and the biological plausibility of an association between Pandemrix and narcolepsy. The meeting counted with the participation of several experts, including paediatric neurologists, epidemiologists, immunologists, vaccinologists, and specialists in sleep disorders and infectious diseases, from a range of EU countries, the European Centre for Disease Prevention and Control (ECDC), and also participants from Health Canada and the World Health Organisation (WHO).

The key conclusions of the meeting included the below:

- The signal of an association between vaccination with Pandemrix and development of narcolepsy with cataplexy in children and adolescents is strong in Sweden and Finland. Appropriate case definitions were used in the studies. There may have been a change in clinical practice towards more rapid diagnosis, however the effect of this, if any, on the magnitude of the risk estimate is currently unclear. Even if a differential diagnostic practice had introduced a bias, such an effect is unlikely to account for the whole signal;
- Environmental factors (such as co-circulating viruses/bacteria) and/or disease modifiers (such as genetic factors) have probably contributed to the shown association. However, as no data are available on possible concurrent exposures which may be relevant, adjustment is not possible and it is unknown whether or not confounding due to such factors may exist;
- At present there is insufficient data from other countries (other than Sweden and Finland) to either confirm or refute the shown association;
- Any further studies should not rely solely on use of electronic primary case databases as these may not include all possible cases – studies should incorporate specialist centres where feasible;

- It is not proven that narcolepsy is an autoimmune condition. However, hypothetical immunological mechanisms through which Pandemrix may theoretically induce narcolepsy were discussed. It was considered that bystander activation could be a plausible autoimmune mechanism, but this would require 'pre-priming' of auto-reactive T cells by other factors. With such a mechanism, the vaccine may be 'triggering' onset of disease in those who have 'built up' susceptibility over several years. It was considered that molecular mimicry was a less plausible mechanism, given that H1N1 has many conserved epitopes which have circulated for decades.

The meeting also advised on issues that should be addressed in any further epidemiological studies, such as better definition of 'at risk' time periods and sensitivity analyses to adjust for potential reporting/diagnostic biases.

### **Upcoming studies**

There are several initiatives being developed across the EU to further investigate the association between Pandemrix and narcolepsy, including case inventory studies being developed by some member states and the ongoing VAESCO study, from which final results are expected.

Exposure to specific infectious diseases (including H1N1) at different ages, particularly upper respiratory infections, raises interesting questions around whether circulating infectious disease may have contributed to the observations in the Nordic area. It is important that ongoing epidemiological studies, including VAESCO, seek to address this question.

In order to avoid an overlap of cases and data-sources, a MAH sponsored epidemiological study will not be conducted in Europe<sup>5</sup>. A retrospective cohort study, including a self-controlled case series (SCCS) analysis and a follow up of cases to assess any atypical or differential clinical course and prognosis in any vaccinated versus non-vaccinated subjects, is being set up in Canada (Quebec). A clinically equivalent GSK AS03-adjuvanted H1N1 vaccine (Arepanrix) was administered to 57% of the population in Canada. These initiatives are reflected in the MAH's risk management plan (RMP). Investigations into any potential biological plausibility of the shown association are ongoing and are further discussed below (see 2.1.4 Biological plausibility). These initiatives are also reflected in the RMP.

#### **1.1.4. Biological plausibility**

The trigger for narcolepsy is currently unclear. There is a known association with human leukocyte antigen (HLA)-DQB1\*0602 in humans, however, the association of DQB1\*0602 is neither necessary nor specific to the development of the condition and it exists at a high prevalence in healthy populations. The possibility of an autoimmune aetiology remains hypothetical, as to date no specific biomarkers or autoantibodies have been identified. Environmental risk factors are also likely important in the aetiology of narcolepsy (and possibly an interplay between genetic and environmental factors).

Molecular mimicry (antigen mimicry between vaccine components and constituents of hypocretin neurons) and non-specific bystander activation were discussed as potential mechanisms for hypothetical vaccine-induced autoimmune narcolepsy. The submitted sequence homology analysis of H1N1 antigen and hypocretin identified no clear evidence to suggest that molecular mimicry is plausible. The lack of a safety signal with other monovalent H1N1 vaccines, including those unadjuvanted vaccines used extensively outside of the European Union, also provides no support for an H1N1 antigen-specific effect.

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<sup>5</sup> The VAESCO consortium is conducting a pooled analysis of cases from population-based healthcare databases in Europe (see 'Retrospective cohort study in Europe – VAESCO')

A potential mechanism for AS03 to induce autoimmunity through general, non-specific bystander activation and/or pre-primed auto-reactive T cells also remains speculative. The AS03 adjuvant contains squalene combined with the surfactant polysorbate 80 to form an emulsion and is used to enhance the immune response. AS03 also contains  $\alpha$ -tocopherol (vitamin E) also used to enhance the immunostimulatory properties of the adjuvant. The available animal toxicity data do not suggest that any of the adjuvant components might play a role in the observed narcolepsy.

However, the MAH will continue to investigate the potential biological plausibility and will conduct non-clinical/clinical (including mechanistic) studies in order to elucidate the role of the vaccine and its adjuvant on the association between Pandemrix and narcolepsy. An experimental plan to test the hypotheses antigen mimicry and bystander activation of pre-primed auto-reactive T-cells is being developed. These studies should also explore any genetic associations.

It is noted that to date there are no suitable autoimmune animal models for narcolepsy. The MAH will also be exploring new models (transgenic mouse model expressing the HLA DQA1\*0102-DQB1\*0602 human allele) for the evaluation of environmental factors in the induction of narcolepsy. If validated, these models may be used to assess whether vaccination with an AS03-adjuvanted pandemic influenza vaccine could induce a change in the hypocretin system and/or local inflammation in the lateral hypothalamus. Studies of T-cell repertoires from adjuvant and non-adjuvant H1N1 vaccine treated human samples are also proposed. This measure was acknowledged by the CHMP and reflected in the RMP.

## **1.2. Discussion**

Observed versus expected analysis from several member states suggest an excess of spontaneous reports following vaccination with Pandemrix. However, given the inherent limitations and potential biases associated with such analyses based on spontaneous data (notably, the likelihood of stimulated reporting, lack of information on reports in unvaccinated subjects and validity of diagnoses), these analysis cannot be used to draw conclusions on causality.

The epidemiological evidence in Finland and Sweden confirms that there is an association between vaccination with Pandemrix and narcolepsy. Results indicate a six to 13-fold increased risk of narcolepsy with or without cataplexy in vaccinated as compared with unvaccinated children/adolescents, corresponding to an absolute risk increase of about three to seven additional cases in 100,000 vaccinated subjects. This risk increase has not been found in adults (older than 20 years).

Although similar epidemiological studies have not been conducted in other EU countries, and the results of the VAESCO initiative are still preliminary, a similar risk cannot be ruled out in other countries. So far, the available data from VAESCO are sufficient only to confirm the increased risk in Finland. The final results of this study are awaited.

Narcolepsy is usually a disease with a long lag time from first symptoms to diagnosis and it is unclear when the 'time at risk' begins, following immunisation. Therefore, the risk window remains unknown presenting a difficulty to establish which cases could be linked to vaccination, even if diagnosed shortly after administration of the vaccine. There was a concern regarding a bias towards rapid diagnosis of vaccinated cases and whether media attention has differentially affected ascertainment of exposed and unexposed cases. Some of the available studies included sensitivity analysis to try to account for potential ascertainment bias due to media attention, and it would be of value to follow this approach and present diagnosis rates over time for all studies. Earlier censoring to avoid the contribution of this bias would however reduce the power of most studies available to date. It was concluded that although

awareness may have contributed to changing diagnostic practice (shortening of lag time between first symptoms and diagnosis and increased use of laboratory tests), the effect of this, if any, on the magnitude of the risk estimate is currently unclear.

It is noted that the vaccine is likely to have interacted with genetic or environmental factors which might raise the risk of narcolepsy. Examples of such factors could be co-circulating viruses/bacteria, as literature suggests that winter infections, such as streptococcal infections as well as influenza, may be associated with development of narcolepsy. There is also some evidence of geographical influences (e.g. by latitude in Sweden) on narcolepsy incidence, but this could not be reproduced in Finland and the relevance of the finding is unclear. Nevertheless, this remains hypothetical as these factors would also not fully explain the observed increased risk.

There remains no evidence of a biological mechanism through which the vaccine and/or its adjuvant may induce narcolepsy. It is also not proven that narcolepsy per se is an autoimmune condition and therefore discussion of potential autoimmune mechanisms remains purely speculative and hypothetical.

The relationship between Pandemrix and narcolepsy is still under investigation, and several studies are ongoing in member states, including the VAESCO study. The possible role of infections or epidemiological, immunological and genetic factors in relation to narcolepsy could be explored. The marketing authorisation holder (MAH) will conduct a retrospective cohort study, including a self-controlled case series (SCCS) analysis, in Canada (Quebec) and a follow-up of cases to assess any atypical or differential clinical course and prognosis in any vaccinated versus non-vaccinated subjects. The MAH will also conduct the necessary non-clinical/clinical (including mechanistic) studies in order to elucidate the role of the vaccine and its adjuvant on the association between Pandemrix vaccination and narcolepsy, as detailed in the risk management plan. However, as the results of these studies may have an impact on the benefit risk balance of Pandemrix, these should also be reflected as conditions to the marketing authorisation. The annex II of the marketing authorisation has been updated accordingly.

The opinion of the expert panel convened on 12 July 2011, on the strength of the epidemiological evidence, potential co-contributory factors and the biological plausibility of an association between Pandemrix and narcolepsy was informative to the Committee.

### **1.3. Risk management plan**

The MAH submitted a risk management plan (RMP), which included a risk minimisation plan. A tabular summary of the RMP, adapted from version 9 dated 17 July 2011 provided for this review is presented below. The new information is presented in the grey shaded text in the table below.

Potential theoretical safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
Anaphylaxis	<ul style="list-style-type: none"> <li>• Enhanced pharmacovigilance               <ul style="list-style-type: none"> <li>○ Weekly signal detection</li> <li>○ Use of targeted follow-up questionnaires</li> <li>○ Individual reports expedited to regulators</li> <li>○ Included in Table 3 of simplified PSURs†</li> <li>○ Cumulative analysis included in full PSUR following end of pandemic period</li> <li>○ Ad hoc analyses if reporting rate exceeds 1/100,000 doses distributed</li> </ul> </li> <li>• Incidence will be estimated in participants of the post-authorisation safety study</li> </ul>	<ul style="list-style-type: none"> <li>• Contraindication in the proposed labelling</li> <li>• Precaution in the proposed labelling regarding use in persons with known hypersensitivity, other than anaphylaxis, to vaccine components</li> </ul>
Autoimmune hepatitis	<ul style="list-style-type: none"> <li>• Enhanced pharmacovigilance               <ul style="list-style-type: none"> <li>○ Weekly signal detection</li> <li>○ Use of targeted follow-up questionnaires</li> <li>○ Individual reports expedited to regulators</li> <li>○ Cumulative analysis included in full PSUR following end of pandemic period</li> <li>○ Ad hoc analyses if reporting rate exceeds 20/100,000 doses distributed</li> </ul> </li> </ul>	NA*
Bell's palsy	<ul style="list-style-type: none"> <li>• Enhanced pharmacovigilance               <ul style="list-style-type: none"> <li>○ Weekly signal detection</li> <li>○ Use of targeted follow-up questionnaires</li> <li>○ Individual reports expedited to regulators</li> <li>○ Included in Table 3 of simplified PSURs</li> <li>○ Cumulative analysis included in full PSUR following end of pandemic period</li> <li>○ Ad hoc analyses if reporting rate exceeds 24/100,000 doses distributed</li> </ul> </li> <li>• Incidence will be estimated in participants of the post-authorisation safety study</li> </ul>	NA
Convulsion	<ul style="list-style-type: none"> <li>• Enhanced pharmacovigilance               <ul style="list-style-type: none"> <li>○ Weekly signal detection</li> <li>○ Use of targeted follow-up questionnaires</li> <li>○ Individual reports expedited to regulators</li> <li>○ Included in Table 3 of simplified PSURs</li> <li>○ Cumulative analysis included in full PSUR following end of pandemic period</li> <li>○ Ad hoc analyses if reporting rate exceeds 3,000/100,000 doses distributed</li> </ul> </li> <li>• Incidence will be estimated in participants of the post-authorisation safety study</li> </ul>	NA

Potential theoretical safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
Demyelinating disorders	<ul style="list-style-type: none"> <li>• Enhanced pharmacovigilance               <ul style="list-style-type: none"> <li>○ Weekly signal detection</li> <li>○ Use of targeted follow-up questionnaires</li> <li>○ Individual reports expedited to regulators</li> <li>○ Included in Table 3 of simplified PSURs</li> <li>○ Cumulative analysis included in full PSUR following end of pandemic period</li> <li>○ Ad hoc analyses if reporting rate exceeds published incidence rate</li> </ul> </li> <li>• Incidence will be estimated in participants of the post-authorisation safety study</li> </ul>	NA
Encephalitis	<ul style="list-style-type: none"> <li>• Enhanced pharmacovigilance               <ul style="list-style-type: none"> <li>○ Weekly signal detection</li> <li>○ Use of targeted follow-up questionnaires</li> <li>○ Individual reports expedited to regulators</li> <li>○ Included in Table 3 of simplified PSURs</li> <li>○ Cumulative analysis included in full PSUR following end of pandemic period</li> <li>○ Ad hoc analyses if reporting rate exceeds 7/100,000 doses distributed</li> </ul> </li> <li>• Incidence will be estimated in participants of the post-authorisation safety study</li> </ul>	NA
Guillain-Barré syndrome	<ul style="list-style-type: none"> <li>• Enhanced pharmacovigilance               <ul style="list-style-type: none"> <li>○ Weekly signal detection</li> <li>○ Use of targeted follow-up questionnaires</li> <li>○ Individual reports expedited to regulators</li> <li>○ Included in Table 3 of simplified PSURs</li> <li>○ Cumulative analysis included in full PSUR following end of pandemic period</li> <li>○ Ad hoc analyses if reporting rate exceeds 2/100,000 doses distributed</li> <li>○ Active monitoring in collaboration with national groups/agencies</li> </ul> </li> <li>• Incidence will be estimated in participants of the post-authorisation safety study</li> <li>• Study to establish a case-series in France, with possibility for case-control analysis, if needed</li> </ul>	NA

Potential theoretical safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
Increased concentrations of hepatic enzymes	<ul style="list-style-type: none"> <li>• Enhanced pharmacovigilance               <ul style="list-style-type: none"> <li>○ Weekly signal detection</li> <li>○ Use of targeted follow-up questionnaires</li> <li>○ Individual reports expedited to regulators</li> <li>○ Cumulative analysis included in full PSUR following end of pandemic period</li> <li>○ Ad hoc analyses if signal detected</li> </ul> </li> </ul>	NA
Neuritis	<ul style="list-style-type: none"> <li>• Enhanced pharmacovigilance               <ul style="list-style-type: none"> <li>○ Weekly signal detection</li> <li>○ Use of targeted follow-up questionnaires</li> <li>○ Individual reports expedited to regulators</li> <li>○ Included in Table 3 of simplified PSURs</li> <li>○ Cumulative analysis included in full PSUR following end of pandemic period</li> <li>○ Ad hoc analyses if reporting rate exceeds published incidence rate</li> </ul> </li> <li>• Incidence will be estimated in participants of the post-authorisation safety study</li> </ul>	NA
Vasculitis	<ul style="list-style-type: none"> <li>• Enhanced pharmacovigilance               <ul style="list-style-type: none"> <li>○ Weekly signal detection</li> <li>○ Use of targeted follow-up questionnaires</li> <li>○ Individual reports expedited to regulators</li> <li>○ Included in Table 3 of simplified PSURs</li> <li>○ Cumulative analysis included in full PSUR following end of pandemic period</li> <li>○ Ad hoc analyses if reporting rate exceeds 2/100,000 doses distributed</li> </ul> </li> <li>• Incidence will be estimated in participants of the post-authorisation safety study</li> </ul>	NA
Vaccination failure	<ul style="list-style-type: none"> <li>• Enhanced pharmacovigilance               <ul style="list-style-type: none"> <li>○ Weekly signal detection</li> <li>○ Use of targeted follow-up questionnaires</li> <li>○ Individual reports expedited to regulators</li> <li>○ Included in Table 3 of simplified PSURs</li> <li>○ Cumulative analysis included in full PSUR following end of pandemic period</li> </ul> </li> <li>• Incidence will be estimated in participants of the post-authorisation safety study</li> </ul>	NA
Vaccine effectiveness	<ul style="list-style-type: none"> <li>• GSK Biologicals will support ECDC vaccine effectiveness project</li> <li>• GSK Biologicals will obtain results from the UK HPA project</li> </ul>	NA

Potential theoretical safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
Fever in children	<ul style="list-style-type: none"> <li>• Additional clinical trials (H1N1-009, H1N1-010, H1N1-012, H1N1-023, H1N1-025)</li> <li>• Routine pharmacovigilance</li> <li>• Cumulative analysis in full PSUR prepared after the pandemic period</li> </ul>	<ul style="list-style-type: none"> <li>• No inclusion of children in the indication section of the proposed labelling</li> <li>• Statement in proposed labelling that there is no experience in children</li> </ul>
Missing data in pregnant women	Routine pharmacovigilance, including follow-up of cases of pregnancy: <ul style="list-style-type: none"> <li>• spontaneously reported by patients and HCPs</li> <li>• enrolled/observed during post-authorisation safety study</li> <li>• observed during clinical trials</li> <li>• reported via Pregnancy Registry</li> </ul>	NA
Missing data in children	Conduct additional clinical trials <ul style="list-style-type: none"> <li>• H1N1-009 (6 to 35 months)</li> <li>• H1N1-010 (3 to 17 years)</li> <li>• H1N1-012 (2 to 5 months)</li> <li>• H1N1-023 (3 to 17 years)</li> <li>• Post-authorisation safety study (depending on UK vaccination policy)</li> </ul>	<ul style="list-style-type: none"> <li>• No inclusion of children in the indication section of the proposed labelling</li> <li>• Statement in proposed labelling that there is no experience in children</li> </ul>
Limited data in subjects with compensated underlying conditions; No data in subjects with severe underlying medical conditions and immunocompromised	<ul style="list-style-type: none"> <li>• Routine pharmacovigilance</li> <li>• Post-authorisation cohort study: individuals will be included based on national recommendations, underlying medical conditions will be documented for <i>post hoc</i> analyses</li> </ul>	NA

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Potential theoretical safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
Narcolepsy	<ul style="list-style-type: none"> <li>Conduct a retrospective cohort study, including a self-controlled case series (SCCS) analysis, in Canada (Quebec) and a follow-up of cases to assess any atypical or differential clinical course and prognosis in any vaccinated vs. non-vaccinated subjects (due date June 2012)</li> <li>Conduct non-clinical/clinical (including mechanistic) studies in order to elucidate the role of the vaccine and its adjuvant on the association between Pandemrix and narcolepsy (due date December 2012)</li> </ul> <p>The above changes are reflected in the annex II**.</p>	<ul style="list-style-type: none"> <li>Change in the following sections of the SPC:               <p><b>Section 4.1</b> Prophylaxis of influenza caused by A (H1N1)v 2009 virus. In persons under 20 years of age, Pandemrix should only be used if the recommended annual seasonal trivalent influenza vaccine is not available and if immunisation against (H1N1)v is considered necessary (see sections 4.4 and 4.8).</p> <p><b>Section 4.4</b> Epidemiological studies relating to Pandemrix in two countries (Sweden and Finland) have indicated a six to 13-fold increased risk of narcolepsy with or without cataplexy in vaccinated as compared with unvaccinated children/adolescents, corresponding to an absolute risk increase of about three to seven additional cases in 100,000 vaccinated subjects. This risk increase has not been found in adults (older than 20 years). A similar risk has not been confirmed but cannot be ruled out in other countries.</p> <p>The relationship between Pandemrix and narcolepsy is still under investigation. In persons under 20 years of age, Pandemrix should only be used if the recommended annual seasonal trivalent influenza vaccine is not available and if immunisation against (H1N1)v is considered necessary. (see section 4.8)</p> <p><b>Section 4.8</b> Very rare<sup>1</sup>: Narcolepsy<sup>2</sup> with or without cataplexy (see section 4.4) <sup>1</sup>frequency based on estimated attributable risk from epidemiological studies in Sweden and Finland (see section 4.4) <sup>2</sup>Reported in subjects below 20 years of age.</p> <p>The PL was updated accordingly.</p> </li> </ul>

SPC: summary of product characteristics; PL: package leaflet.

\* NA = not applicable; † PSUR = periodic safety update report

\*\*The CHMP, having considered the data submitted, was of the opinion that these pharmacovigilance activities in addition to the use of routine pharmacovigilance are needed to investigate further some of the safety concerns. Updates are to be submitted in accordance with the timelines specified in the RMP.

## **1.4. Product information**

The CHMP proposed to update the summary of product characteristics (SPC) to reflect the below information.

Section 4.1 of the SPC was updated to reflect a modification to the indication. In persons under 20 years of age Pandemrix should only be used if the recommended annual seasonal trivalent influenza vaccine is not available and if immunisation against (H1N1)v is considered necessary.

Section 4.4 of the SPC was revised to reflect on updated information regarding epidemiological studies relating to the association between vaccination with Pandemrix and narcolepsy.

Section 4.8 of the SPC was updated to include narcolepsy with a frequency of 'very rare'.

The annex II was updated to reflect the conditions to the marketing authorisation. Other minor changes were included to bring this section up to date with the latest templates and to delete obsolete information regarding submission of studies which were already submitted for review.

The PL was updated in line with the changes to the SPC.

## **2. Overall discussion and benefit/risk assessment**

Pandemrix is a (H1N1)v split virion, inactivated, adjuvanted influenza vaccine, authorised for prophylaxis of influenza caused by A (H1N1)v 2009 virus.

On 27 August 2010 a review of Pandemrix was initiated at the request of the European Commission pursuant to Article 20 of Regulation (EC) No 726/2004. The concern arose from spontaneous case reports of narcolepsy in Finland and Sweden which suggested a signal of excess reports following vaccination with Pandemrix. The signal was apparent only amongst children and adolescents aged 4-19 years, with no clear excess reporting in adults.

An epidemiological study in Finland conducted by the Finnish National Institute for Health and Welfare (THL) compared the incidence of narcolepsy in people vaccinated with Pandemrix between 1 January 2009 and 31 December 2010, with the incidence of narcolepsy in unvaccinated people of the same age. The study cohort included 915,854 subjects born between 1991 and 2005. During the study period, 70.6% subjects were vaccinated with Pandemrix and 29.4% were never vaccinated. Vaccinated subjects contributed risk time in the unvaccinated group until the time point at which they were vaccinated. The study considered the date of first health care visit with symptoms of narcolepsy. The main analysis (preliminary results) found an increased relative risk of narcolepsy in the vaccinated group of 9.2 (95% CI: 4.5-21.4) for vaccinated children/adolescents as compared with non-vaccinated. Among persons over 19 years of age the incidence of narcolepsy was not shown to increase.

Final results showed a relative risk ratio in the vaccinated group of 12.7 (95% CI: 6.1-30.8).

A similar epidemiological study conducted in Sweden by the Medical Products Agency (MPA) compared the incidence of narcolepsy in individuals resident in four counties/regions on 1 October 2009 (representing 57% of the Swedish population). All subjects registered in the respective county on 1 October 2009 without a known diagnosis of narcolepsy were followed until 31 December 2010, date of narcolepsy diagnosis, death or migration from the county, whichever came first. In the cohort of vaccinated subjects the follow-up time was defined as exposed from the date of vaccination until the end of follow-up. Vaccinated subjects contributed with exposure time in the unvaccinated group from 1

October 2009 to the date of vaccination. The main analysis, found an increased relative risk of narcolepsy in the vaccinated group of 4.19 (95% CI: 1.76-12.1) for vaccinated children/adolescents as compared with non-vaccinated. Among persons over 20 years of age the incidence of narcolepsy was not shown to increase.

In addition to the retrospective cohort study, a recently available case inventory study investigated the association between Pandemrix and reports of narcolepsy in Sweden. The study compared the incidence of narcolepsy with cataplexy in subjects vaccinated with Pandemrix with unvaccinated subjects during the pandemic period and thereafter. The study focused on children/adolescents, as there is no evidence to date of an increased risk for narcolepsy in adults. A total of 81 cases of narcolepsy with cataplexy were identified for the whole study period of which 69 had been vaccinated before the onset of the first symptom, compared with 7 unvaccinated cases occurring during the pandemic period. The incidence rate showed an increased relative risk of 6.6 (95% CI: 3.1-14.5) in those vaccinated compared to the non-vaccinated subjects and an absolute risk of 3.6 additional cases (95% CI: 2.5-4.7) per 100,000 vaccinated subjects.

The Vaccine Adverse Event Surveillance and Communication (VAESCO) consortium study is being conducted in Denmark, Finland, France, Italy, The Netherlands, Norway, Sweden, and the United Kingdom. The specific objectives were to assess the background rate of narcolepsy (2000 to 2010), a potential change in narcolepsy rates after April 2009 and the potential association between risk factors including influenza, infections vaccinations and narcolepsy. Preliminary results now available showed that incidence rates are age dependent with the highest peak observed between 15-35 years of age, and with an annual winter peak. Based on the available background rates, a signal of increasing incidence of narcolepsy diagnoses after the start of the H1N1 vaccination campaign could be observed only in Finland in children/adolescents 5-19 years of age, and further data is being collected from other member states.

The analysis for the case control study included all collected cases. Fifty three cases of narcolepsy from Finland and Sweden were included in the analysis (41 in children and adolescents). From other countries, 44 cases were available (17 children and adolescents). The primary analysis in all ages resulted in overall matched estimates for the association between H1N1 vaccination exposure and narcolepsy of 5.61 for Finland (95%CI: 1.24-25.4) and 2.03 for Sweden (0.20-20.3). For The Netherlands the estimate was 3.2 (0.3-39). Estimates could not be calculated for Denmark, Italy and the UK separately as there was no exposure in cases. Pooling of data from the non-signalling countries yielded an overall matched odds ratio of 1.84 (95%CI: 0.21-15.9).

The signal of an association between pandemic H1N1 vaccination and narcolepsy was confirmed in Finland, with preliminary results stratified by age showing an overall risk of 6.34 (95%CI: 1.29-31.2). The estimated risk ratio was lower than the risk ratio of the generating cohort study. This could be due to adjustment for age, sex and calendar time in the case control study, and the slightly different age cut (5-18 years of age) and censoring (period up to July, instead of August). The signal was not significant in Sweden, but only partial data has been collected so far. No association between pandemic H1N1 vaccination and narcolepsy was observed in adults. The number of exposed cases was very limited outside of these countries, therefore no estimate could be calculated for children /adolescents.

Complete data collection on cases and controls is not yet achieved. Once these data are available, VAESCO will conduct fully adjusted analysis including for infections and other vaccinations. The study will also explore how media attention may have affected the results.

The CHMP sought the opinion of an expert panel on 12 July 2011, on the strength of the epidemiological evidence, potential co-contributory factors and the biological plausibility of an association between Pandemrix and narcolepsy. Experts from a range of EU countries, the European Centre for Disease Prevention and Control (ECDC), and also participants from Health Canada and the

World Health Organisation (WHO) were invited. The outcome of this meeting was informative to the Committee.

The CHMP acknowledged that the epidemiological studies were well-designed and used the appropriate standards of diagnosis.

It was concluded that although awareness may have contributed to changing diagnostic practice (shortening of time between first symptoms and diagnosis and increased use of laboratory tests), the effect of this, if any, on the magnitude of the risk estimate is currently unclear. It is noted that the vaccine is likely to have interacted with genetic or environmental factors which might raise the risk of narcolepsy. Examples of such factors could be co-circulating viruses/bacteria, as literature suggests that winter infections, such as streptococcal infections as well as influenza, may be associated with development of narcolepsy. There is also some evidence of geographical influences (e.g. by latitude in Sweden) on narcolepsy incidence, but this could not be reproduced in Finland and the relevance of the finding is unclear. Nevertheless, this remains hypothetical as these factors would also not fully explain the observed increased risk.

Based on all available evidence, the CHMP concluded that the results of these studies suggest an association between Pandemrix vaccination and narcolepsy in children and adolescents in Finland and Sweden, with a six to 13-fold increased risk of narcolepsy with or without cataplexy in vaccinated as compared with unvaccinated subjects. This corresponds to a frequency of 'very rare', and an absolute risk increase of about three to seven additional cases in 100,000 vaccinated subjects. This risk increase has not been found in adults (older than 20 years). A similar risk has not been confirmed but cannot be ruled out in other countries. The preliminary results of the VAESCO study confirmed the association between vaccination with Pandemrix and narcolepsy in Finland but insufficient data is available from other member states to confirm or refute this finding.

The Committee recommended that, in persons under 20 years of age, Pandemrix should only be used if the recommended seasonal trivalent influenza vaccine is not available and if immunisation against H1N1 is considered necessary. The product information was updated to reflect the change to the therapeutic indication, the revision of the warning on narcolepsy and the addition of narcolepsy as an undesirable effect with a frequency of 'very rare'.

The relationship between Pandemrix and narcolepsy is still under investigation and research efforts are needed. Several initiatives are critical to the understanding of this association. In particular, the marketing authorisation holder will conduct a retrospective cohort study in Canada (Quebec). The company will also conduct the necessary non-clinical/clinical studies in order to elucidate the role of the vaccine and its adjuvant on the association between vaccination with Pandemrix and narcolepsy.

### **Benefit/risk balance**

Taking all the above into account, the CHMP considered that the benefit risk balance for Pandemrix is positive in the approved revised indication. Pandemrix is indicated in the prophylaxis of influenza caused by A (H1N1)v 2009 virus. In persons under 20 years of age, Pandemrix should only be used if the recommended annual seasonal trivalent influenza vaccine is not available, and if immunisation against H1N1 is considered necessary.

### 3. Overall conclusion

Based on the review of data submitted by the MAH, as well as data from available epidemiological studies, analysis of safety surveillance data, case reports from across the EU and the outcome of an expert meeting, the CHMP considers that the benefit risk balance of Pandemrix is positive in the revised indication, *i.e.* ". Prophylaxis of influenza caused by A (H1N1)v 2009 virus. In persons under 20 years of age, Pandemrix should only be used if the recommended annual seasonal trivalent influenza vaccine is not available and if immunisation against (H1N1)v is considered necessary (see sections 4.4 and 4.8). Pandemrix should be used in accordance with Official Guidance"

Epidemiological studies relating to Pandemrix in two countries (Sweden and Finland) have indicated a six to 13-fold increased risk of narcolepsy with or without cataplexy in vaccinated as compared with unvaccinated children/adolescents, corresponding to an absolute risk increase of about three to seven additional cases in 100,000 vaccinated subjects. This risk increase has not been found in adults (older than 20 years). A similar risk has not been confirmed but cannot be ruled out in other countries. Pandemrix is indicated in the prophylaxis of influenza caused by A (H1N1)v 2009 virus. In persons under 20 years of age, Pandemrix should only be used if the recommended annual seasonal trivalent influenza vaccine is not available and if immunisation against (H1N1)v is considered necessary.

The relationship between Pandemrix and narcolepsy is still under investigation and several initiatives are critical to the understanding of this association. In particular, the marketing authorisation holder will conduct a retrospective cohort study in Canada. The company will also conduct the necessary non-clinical/clinical studies in order to elucidate the role of the vaccine and its adjuvant on the association between vaccination with Pandemrix and narcolepsy. As the results of these studies may have an impact on the benefit risk balance of Pandemrix, these should be reflected as conditions to the marketing authorisation, as follows:

#### Obligation to complete post-authorisation measures

The MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
Conduct a retrospective cohort study, including a self-controlled case series (SCCS) analysis, in Canada (Quebec) and a follow-up of cases to assess any atypical or differential clinical course and prognosis in any vaccinated vs. non-vaccinated subjects.	June 2012
Conduct non-clinical/clinical (including mechanistic) studies in order to elucidate the role of the vaccine and its adjuvant on the association between Pandemrix and narcolepsy.	December 2012

Therefore the CHMP recommends the variation of the marketing authorisation for which the annex I, II and IIIB are set out in the annexes of the opinion.

## 4. Conclusion and grounds for the recommendation

The Committee considered the procedure under Article 20 of Regulation (EC) No 726/2004, for Pandemrix initiated by the European Commission;

The Committee considered all data submitted by the MAH, as well as data from available epidemiological studies, analysis of safety surveillance data, case reports from across the EU and the outcome of an expert meeting;

The Committee concluded that the data show an association between vaccination with Pandemrix and narcolepsy. An increased risk of narcolepsy with or without cataplexy following vaccination with Pandemrix is confirmed by available epidemiological evidence in children and adolescents up to 19 years of age in Finland and Sweden. A similar risk has not been confirmed but cannot be ruled out in other countries.

The Committee concluded that in persons under 20 years of age, Pandemrix should only be used if the recommended annual seasonal trivalent influenza vaccine is not available and if immunisation against (H1N1)v is considered necessary. The product information (SPC and PL) was amended accordingly.

The relationship between Pandemrix and narcolepsy is still under investigation. The MAH will conduct a retrospective cohort study in Canada, where a clinically equivalent vaccine was widely used. The MAH will also carry out non-clinical/clinical studies in order to further explore the association between vaccination with Pandemrix and narcolepsy. As these studies are critical the CHMP recommended that these were reflected as conditions in the annex II.

The Committee concluded that the benefits still outweighs the risks in the revised therapeutic indication for Pandemrix, and therefore the marketing authorisation is maintained.

Divergent positions are presented in the appendix.

Medicinal product no longer authorised

**Appendix**

DIVERGENT POSITIONS

The undersigned CHMP Delegates expressed divergent views with regards to the Opinion given by the CHMP within the Article 20 procedure for Pandemrix vaccine. The reasons for the divergent views are summarised as follows:

**Grounds for divergent Opinion**

- The results from the epidemiological studies performed in Sweden and Finland strongly suggest a relationship between Pandemrix and narcolepsy in children and adolescents. Taking the current non-pandemic H1N1 situation in Europe into consideration, we are of the opinion that a clear precautionary approach is warranted i.e. restricting the use to adults only.

**CHMP members expressing a divergent opinion:**

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Piotr Fiedor

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Jan Mazag

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Tomas Salmonson

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Barbara van Zwieten-Boot

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Alar Irs

The undersigned CHMP Delegate expressed divergent views with regards to the Opinion given by the CHMP within the Article 20 procedure for Pandemrix vaccine. The reasons for the divergent views are summarised as follows:

**Grounds for divergent Opinion**

- The results from the epidemiological studies performed in Sweden and Finland strongly suggest a relationship between Pandemrix and narcolepsy in children and adolescents. Taking the current non-pandemic H1N1 situation in Europe into consideration, we are of the opinion that a clear precautionary approach is warranted i.e. restricting the use to adults only.

**CHMP member expressing a divergent opinion:**

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Kolbeinn Guðmundsson

Medicinal product no longer authorised