It should be emphasised that in any case the use of Pandemrix in place of a seasonal influenza vaccine is hypothetical, as currently no doses of Pandemrix remain on the market and the MAH has no plans to manufacture any further batches.

On the basis of their assessment considering Pandemrix use in a seasonal context, which is at least a theoretical possibility, the MAH now agrees to the previous CHMP proposal to restrict the indication of Pandemrix to state that it should only be used if the recommended annual seasonal influenza vaccines are not available, and if immunisation against (H1N1)v is considered necessary.

Regarding research into a potential mechanism for the Pandemrix and narcolepsy association, of molecular mimicry involving epitopes on hypocretin neurons and the H1N1 antigen, which is mentioned by the MAH, this will be discussed in the context of an upcoming assessment to the CHMP following the MAH's submission of an updated narcolepsy investigation program in variation II-74.

2.3. Risk management plan

The MAH submitted with this variation application version 17 of the Pandemrix RMP. The RMP includes an updated discussion of narcolepsy with data from Swedish, Finnish and French adult studies, high-level results from the non-clinical research to evaluate potential H1N1/human shared CD4 T cells epitopes (molecular mimicry), details of the updated benefit-risk assessment for Pandemrix, and changes relating to the proposed restricted indication to adults ≥18 years in a pandemic situation.

In addition, the RMP has been further updated related to the study assessed in variation II/67, concerning results of a self-controlled case series in CPRD on the potential risk of transplant rejection following Pandemrix and II/68, concerning results of the additional test-negative case-control analysis from the Quebec narcolepsy study. The PRAC considered during its March 2014 meeting that the MAH should submit an updated version of the RMP to reflect the requests for revisions to the product information from variation II-69. The updated RMP (version 18) is currently under assessment within variation II/74 (Update of the MAH's research plan reflected in Annex II to conduct non-clinical (including mechanistic) studies in order to elucidate the role of the vaccine and its adjuvant on the association between Pandemrix and narcolepsy).

2.4. Changes to the Product Information

As a result of the re-assessment of the benefit-risk and restriction of the indication, the MAH initially proposed the following changes to the Product Information (PI):

SmPC

- **Section 4.1**: Reflection of restriction of indication to adults ≥18 years and only in an officially declared pandemic situation

Prophylaxis of influenza in adults 18 years of age and older in an officially declared pandemic situation 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).~~

- **Section 4.2**: Removal of dosing information relating to children and adolescents, addition of a statement that Pandemrix is not recommended in children and adolescents aged below 18 years.
- **Section 4.4**: removal of information relating to the paediatric population (paragraph on intensity of side effects such as fever after second dose) and revision of paragraph on the risk of narcolepsy:

'Epidemiological studies ~~relating to Pandemrix~~ in several European countries have reported an association between Pandemrix and narcolepsy ~~indicated a five to 14-fold increased risk of narcolepsy~~ with or without cataplexy. These studies have described an absolute risk increase of narcolepsy of approximately 1.4 to 8

additional cases per 100,000 vaccinated children/adolsecents and approximately 1 additional case per 100,000 vaccinated adults compared to background rates of 0.12 to 0.79 per 100,000 children/adolescents per year and 0.67 to 1.10 per 100,000 adults per year. Further research is needed to investigate the observed association between Pandemrix and narcolepsy.
~~*in vaccinated as compared with unvaccinated children/adolescents, corresponding to an absolute risk ranging from three to seven additional cases in 100 000 vaccinated subjects. This risk increase has not been found in adults (older than 20 years).*~~

~~*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)'*~~

The MAH explained that for the sake of simplicity, only the absolute risk of narcolepsy per 100,000 are retained in the proposal for section 4.4 as they consider this to be the most clinically relevant information. The MAH also proposes to include background incidence rates to provide a baseline for the additional cases of narcolepsy reported. The MAH explains that these rates were taken from a publication by Wijnan et al. (Vaccine. 2013).

- **Section 4.8**: Removal of information on adverse effects in the paediatric population (febrile convulsions, tables of ADRs from clinical studies).
- **Section 5.1**: Removal of paediatric immunogenicity data.
- **Annex II**: removal of the commitment to perform a re-analysis of the Quebec narcolepsy dataset with adjustment for medically-attended respiratory infection/influenza like illness.

Description	Due Date
Conduct a retrospective epidemiological study in Canada (Quebec) and follow-up cases to assess any atypical or differential clinical course and prognosis in any vaccinated vs. non-vaccinated subjects: - Test-negative case-control study results ~~- Re-analysis of the dataset with adjustment for medically-attended respiratory infection/influenza-like illness~~ - Re-analysis of the dataset after exclusion of symptomatic controls after 1 year follow-up (if applicable); and description of the clinical follow-up of cases for 2 years	December 2013 ~~December 2013~~ December 2014
Conduct non-clinical (including mechanistic) studies in order to elucidate the role of the vaccine and its adjuvant on the association between Pandemrix and narcolepsy: - If deep sequencing approach is proven feasible: o identify T cell signature from narcoleptic patients and, if identified, verify if signature is found in CD4 T cells from healthy vaccinees o if identified, verify if T cell signature is detected in influenza-specific CD4 T cells from narcoleptic patients - Establish influenza-specific T cell lines to evaluate potential cross-reactivity with hypocretin peptides, with identified DQ*0602 binders and with additional proteins using T2 cells as antigen-presenting cells - Conduct a study in cotton rats to evaluate the potential impact of Pandemrix vaccination/H1N1v infection on the blood-brain-barrier integrity and CNS inflammation/damage. - 'Evaluate the potential for immunological differences between Pandemrix and Arepanrix H1N1 using antibody avidity analysis and phage display-assisted epitope mapping from clinical serum samples obtained before and at Day 21 after vaccination from clinical studies in which the two vaccines were compared.	June 2014 December 2014 December 2014 June 2014 December 2014

During the procedure, the CHMP did not accept the MAH's initial proposal for the restriction of the indication and requested additional amendments to the Product Information. The premise of the MAH's quantitative benefit assessment and proposed indication, i.e. that Pandemrix may offer benefits in a future pandemic, was considered invalid by the CHMP. This assessment can only be undertaken on the basis of the currently approved indication. As no new data have been presented that would affect the potential, benefits of the vaccine to individuals (notwithstanding the fact that the vaccine is no longer in use and TIV/QIV are the vaccines of choice), and as no significant new data have been presented on the attributable risk of narcolepsy, there is little basis to alter the current conclusion on the indication as reached by PRAC / CHMP in June 2013.

Therefore, the MAH's proposal for section 4.1, and hence, the proposal to remove all paediatric data from the product information was not accepted.

Moreover, the MAH's proposal for section 4.4 was not considered to be justified and therefore the MAH was requested to adopt the narcolepsy paragraph proposed by the PRAC /CHMP in June 2013, with some amendments to the risk estimates. The MAH was also requested to amend section 2 of the PL in accordance with the requested SmPC revisions.

As discussed above, the MAH agreed to amend the wording of the Pandemrix indication to restrict its use as a seasonal vaccine only if seasonal influenza vaccines are not available, as requested by the CHMP in June 2013. The minor modification to include reference to quadrivalent seasonal influenza vaccines is accepted.

In addition, The MAH agreed to the PRAC-proposed wording for section 4.4 of the Pandemrix SmPC. The rationale for the slight amendment to the statement on declining risk with increasing age at vaccination is acknowledged, and the modification is accepted.

The proposal to add reference to seasonal quadrivalent influenza vaccines in the context of availability of seasonal vaccines is agreed.

Although not discussed in the MAH's responses, as per the CHMP request from June 2013, the MAH has removed from section 4.8 of the SmPC, the footnote to table of ADRs which indicates that narcolepsy has only been reported in those below 20 years, which is considered acceptable.

The MAH has also adopted the wording requested by CHMP for the package leaflet to reflect the SmPC changes accordingly.

The proposal to remove from Annex II, the commitment to perform a re-analysis of the Quebec narcolepsy dataset with adjustment for medically-attended respiratory infection/influenza like illness is also accepted.

Please refer to attached highlighted version of the product information for further details.

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

As requested by the CHMP in March 2014, the MAH submitted in the context of this type II variation, a benefit-risk assessment of Pandemrix when used in a hypothetical scenario as a seasonal vaccine for prophylaxis against A (H1N1)09–related infections and proposed to update the Pandemrix product information to reflect the totality of epidemiological evidence on the association between the vaccine and narcolepsy.

Notwithstanding that only a qualitative assessment has been provided due to lack of data on Pandemrix use as a seasonal influenza vaccine (although the indication permits seasonal use, the vaccine had not been used since 2011 and all doses on the market expired some time ago), involving a range of assumptions from level of disease burden to vaccine uptake, it is acknowledged that the A (H1N1)09 continues to circulate globally and contribute to a substantial amount of the disease burden associated with influenza infection. It is also acknowledged that available immunogenicity and efficacy data for Pandemrix support the beneficial effects that this vaccine could offer the general population in the event of unavailability of alternative seasonal tri-and quadrivalent influenza vaccines, in particular for certain vulnerable populations (pregnant women, the elderly and immunocompromised individuals). The main risk associated with Pandemrix is that of narcolepsy, with epidemiological studies suggesting a vaccine attributable risk 1 to 8 additional cases per 100,000 persons.

As a result of the MAH's additional benefit-risk assessment, the MAH agrees to the CHMP proposed revisions to the Pandemrix SmPC and PIL (to remove the age restriction of 20 years from section 4.1, to remove the sentence on [no increased risk of] narcolepsy in adults and to revise the narcolepsy warnings to reflect the current totality of epidemiological data on Pandemrix and narcolepsy). The MAH also proposed some minor modifications to the wording which is accepted. Taking into account the safety data submitted and their reflection in the Product Information in terms of a restriction of the indication, the CHMP considers that the benefit-risk balance for Pandemrix is favourable in the restricted indication.

4. Recommendations

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation(s) to the terms of the Marketing Authorisation, concerning the following change(s):

Variation(s) requested		Type
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

To revise the indication to reflect that Pandemrix should only be used for prophylaxis of influenza caused by A(H1N1)v 2009 if recommended seasonal influenza vaccine is not available and immunisation against A(H1N1)v 2009 is considered necessary, to update sections 4.4 and 4.8 of the SmPC to reflect the totality of the data on the risk of narcolepsy and to provide an updated benefit-risk assessment of Pandemrix, based on the data currently available to the MAH on H1N1 influenza disease burden, effectiveness and safety of Pandemrix and available epidemiology data on narcolepsy. The Package Leaflet is updated accordingly.

The MAH also took the opportunity to update the list of 'Obligation to conduct post-authorisation measures' in Annex II to remove the condition "Re-analysis of the dataset with adjustment for medically-attended respiratory infection/influenza-like illness" as the MAH will not be in a position to fulfil this request.

The requested variation proposed amendments to the Summary of Product Characteristics, Annex II and Package Leaflet.

Conditions and requirements of the marketing authorisation

- **Obligation to conduct post-authorisation measures**

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

Description	Due Date
Conduct a retrospective epidemiological study in Canada (Quebec) and follow-up cases to assess any atypical or differential clinical course and prognosis in any vaccinated vs. non-vaccinated subjects: - Test-negative case-control study results - Re-analysis of the dataset after exclusion of symptomatic controls after 1 year follow-up (if applicable); and description of the clinical follow-up of cases for 2 years.	 December 2013 December 2014
Conduct non-clinical (including mechanistic) studies in order to elucidate the role of the vaccine and its adjuvant on the association between Pandemrix and narcolepsy: - If deep sequencing approach is proven feasible: o identify T cell signature from narcoleptic patients and, if identified, verify if signature is found in CD4 T cells from healthy vaccinees o if identified, verify if T cell signature is detected in influenza-specific CD4 T cells from narcoleptic patients - Establish influenza-specific T cell lines to evaluate potential cross-reactivity with hypocretin peptides, with identified DQ*0602 binders and with additional proteins using T2 cells as antigen-presenting cells - Conduct a study in cotton rats to evaluate the potential impact of Pandemrix vaccination/H1N1v infection on the blood-brain-barrier integrity and CNS inflammation/damage. - 'Evaluate the potential for immunological differences between Pandemrix and Arepanrix H1N1 using antibody avidity analysis and phage display-assisted epitope mapping from clinical serum samples obtained before and at Day 21 after vaccination from clinical studies in which the two vaccines were compared.	 June 2014 December 2014 December 2014 June 2014 December 2014

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