NOTE:

COMMERCIALLY CONFIDENTIAL INFORMATION HAS BEEN REMOVED FROM THIS DOCUMENT.

ANNEX I

List of the names, pharmaceutical forms, strengths of the medicinal products, route of administration, marketing authorisation holders in the member states

Member State (in EEA)	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical form	Route of administration
Austria	Baxter AG Industriestrasse 67 Vienna 1221 Austria	Preflucel Injektionssuspen sion in einer Fertigspritze	15 micrograms haemagglutinin of each of the 3 specified strains as determined by WHO per 0.5 ml dose	suspension for injection in a pre-filled syringe	intramuscular use
Belgium	Baxter S.A. Bd René Branquart 80 7860 Lessines Belgium	Preflucel	15 µg-0,5 ml	suspension for injection	intramuscular use
Czech Republic	Baxter AG Industriestrasse 67 Vienna 1221 Austria	PREFLUCEL	0,5 ml per dose	suspension for injection	intramuscular use
Denmark	Baxter A/S Gydevang 43 DK-3450 Allerød Denmark	Preflucel	15 microgram	suspension for injection in a prefilled syringe	intramuscular use
Finland	Baxter Oy Tammasaarenkatu 1 PL 119 00181 Helsinki Finland	Preflucel	15 mikrog HA / 0,5 ml 15 mikrog HA / 0,5 ml 15 mikrog HA / 0,5 ml	suspension for injection in pre-filled syringe	intramuscular use

Member State (in EEA)	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical form	Route of administration
Germany	Baxter Deutschland GmbH Edisonstraße 4 85716 Unterschleißheim Germany	PREFLUCEL	15 µgHA 15 µgHA 15 µgHA	suspension for injection in prefilled syringe	intramuscular use
Ireland	Baxter Healthcare Limited Caxton Way Thetford Norfolk IP24 3SE United Kingdom	Preflucel suspension for injection in a pre- filled syringe	15 microgram	suspension for injection	intramuscular use
Italy	Baxter S.p.A. Piazzale dell'Industria 20 Rome 00144 Italy	PREFLUCELL	15 micrograms	suspension for injection in a pre-filled syringe	intramuscular use
Norway	Baxter AS Gjerdrums vei 11 N-0484 Oslo Norway	Preflucel	15 µg hemagglutinin of each of the 3 influenza virus strains	suspension for injection in a pre-filled syringe	intramuscular use
Poland	Baxter Polska Sp. z o.o. Kruczkowskiego 8 00-380 Warszawa Poland	Preflucel	A/California/07/2009 (H1N1) - 15 micrograms HA A/Perth/16/2009 (H3N2) like strain used (A/Victoria/210/2009)- 15 micrograms HA B/Brisbane/60/2008 (B)- 15 micrograms HA/ HA** per 0.5 ml dose	suspension for injection in a pre-filled syringe	intramuscular use

Member State (in EEA)	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical form	Route of administration
Portugal	Baxter Médico-Farmacêutica, Lda. Zona Industrial da Abrunheira Edifício 10 Sintra Business Park 2710-089 Sintra Portugal	Preflucel	A/California/7/2009 (H1N1) - like virus → 0.015 mg A/Perth/16/2009 (H3N2) - like virus → 0.015 mg B/Brisbane/60/2008 → 0.015 mg	suspension for injection in a pre-filled syringe	intramuscular Use
Spain	Baxter, S.L. Polígono Industrial Sector 14 Pouet de Camilo, 2 Ribarroja del Turia Valencia 46394 Spain	PREFLUCEL SUSPENSION INYECTABLE EN JERINGA PRECARGADA	A/California/07/2009 (H1N1) - 15 micrograms HA; A/Perth/16/2009 (H3N2) like strain used: (A/Victoria/210/2009)- 15 micrograms HA; B/Brisbane/60/2008 (B)- 15 micrograms HA, per 0.5 ml dose	suspension for injection in prefilled syringe	intramuscular use
Sweden	Baxter Medical AB Torshamnsgatan 35 Box 63 164 94 Kista Sweden	Preflucel	(NA)	solution for injection, pre filled syringe	intramuscular use
The Netherlands	Baxter B.V. Kobaltweg 49 3542 CE Utrecht The Netherlands	Preflucel 2011/2012, suspensie voor injectie 0,5 ml	0,5 ml per dose	suspension for injection	intramuscular use
United Kingdom	Baxter Healthcare Limited Caxton Way Thetford Norfolk IP24 3SE United Kingdom	Preflucel	15 mcg hemagglutinin of each of the 3 influenza virus strains	suspension for injection in a pre-filled syringe	intramuscular use

Annex II

Scientific conclusions and grounds for maintenance of the marketing authorisation subject to conditions

Scientific conclusions and grounds for maintenance of the marketing authorisations subject to conditions

Overall summary of the scientific evaluation of Preflucel and associated names (See Annex I)

Preflucel is a Vero cell-based seasonal, split, non-adjuvanted influenza vaccine indicated in prophylaxis for influenza in adults.

The Influenza purified antigen containing medicinal products, Preflucel and associated names, are authorised in Austria (acting as Reference Member State), Czech Republic, Belgium, Germany, Denmark, Spain, Finland, Ireland, Italy, Netherlands, Norway, Poland, Portugal, Sweden and United Kingdom (see Annex I for the list of Preflucel and associated names authorised in the EU) through decentralised and repeat use procedures.

On 20 October 2011, the Austrian National Competent Authority informed the Member States and the European Medicines Agency via a NUI (Non Urgent Information) about a voluntary recall from the Marketing Authorisation Holder (Baxter) of one batch of Preflucel (batch VNV5L010, manufactured on 09 August 2011) due to a possible emerging safety signal, which was identified based on an increased number of adverse event case reports associated with this batch. Adverse reactions such as hypersensitivity reactions (including anaphylactic reactions), influenza-like- symptoms and ocular reactions were reported in a frequency higher than expected following administration of at least that identified batch of Preflucel. This batch (VNV5L010) predominated on the European market with 127.306 doses distributed at the time but increased reporting rates were also observed with the batch VNV5L012 (batch with the second highest distribution e.g. with 98.084 doses).

Investigations performed by the MAH at the time led to the conclusion that the residual trypsin activity could be correlated to the observed adverse reactions and that other parameters (such as aggregates or whole virus particles, high haemagglutinin levels or age of monovalent bulk) were possibly triggering these undesirable events. GMP inspections were also performed at the manufacturing sites in Bohumil and Vienna during which no process related issues with potential impact on the current adverse events were identified.

Therefore on 24 October 2011, the Austrian National Competent Authority informed the Member States and the European Medicines Agency via an updated NUI that the root cause of this observation had not been identified so far and that the MAH voluntarily agreed to recall all distributed batches (batches VNV5L011, VNV5L012 and VNV5L013 in addition to batch VNV5L010) from the European market as a precautionary measure.

Since then no product has been released to the market. Preflucel is a flu vaccine and therefore application for yearly strain changes need to be approved by the Competent Authority and batches need to be released by the Competent OMCL before being placed to the market.

The Austrian Authority was of the opinion that the root cause of the adverse reactions of the product and the substitution to an alternative manufacturing process for Preflucel with appropriate controls to effectively reduce this risk had to be further evaluated.

Therefore on 09 December 2011 Austria referred the matter to the CHMP so that the Committee could conduct an EU review of the root cause and issue an opinion on whether the marketing authorisation of Preflucel should be maintained, varied, suspended or withdrawn. Consultation of the Biologics Working Party was requested by the CHMP.

Scientific discussions

Hypersensitivity reactions (including 4 confirmed out of 6 identified anaphylactic reactions), influenza-like-illness including fever, chills, headache, malaise, nausea and fatigue and ocular reactions were reported in a frequency higher than expected following administration of at least the identified batch VNV5L010 of Preflucel:

1. Hypersensitivity events were identified by a database Preferred Term (PT) query for anaphylactic reaction/shock and/or hypersensitivity as well as using the Standardized MedDRA Query (SMQ) Anaphylactic reaction. All cases that were retrieved by this SMQ were evaluated according to Brighton case definitions, as well as according to Ring and Messmer (Ring et al. 2010).
2. For influenza like-illness events, a PT query was also performed. In addition, the European case definition for influenza-like illness (ILI) was used to identify additional cases reported during post-marketing. A case of influenza like illness (ILI) is defined as an individual presenting a sudden onset of symptoms and at least one of the following four systemic symptoms: fever (≥ 38.0 °C) or feverishness; malaise; headache, myalgia and at least one of the following three respiratory symptoms: cough; sore throat; and shortness of breath.
3. Finally the ocular events were identified as all cases that had at least one term (PT) corresponding to the System Organ Class (SOC) Eye disorders.

No process related issues with potential impact on the current adverse events was identified during the GMP inspections performed at the manufacturing sites (Bohumil, Vienna). Hence the root cause analysis led the MAH to investigate the potential parameters triggering these undesirable events i.e. the residual trypsin activity and some other factors such as aggregates or whole virus particles, high haemagglutinin levels or stability of monovalent bulk.

The MAH provided investigation reports on the biochemical and technical root cause analysis in order to explain the observed increased adverse reactions reporting rate.

Biochemical and technical root cause

To identify the potential root cause for the observed increased number of adverse event (AE) of Preflucel batch VNV5L010, the MAH performed a broad quality and manufacturing investigation including multi-variant data analysis (MVDA) and process monitoring. Data on process monitoring was included for all produced Preflucel lots of the season 2011/2012 and the marketed Preflucel lot of the season 2010/2011.

The MAH has provided extensive quality data including repeated release testing results of 2011/2012 season lots VNV5L010, VNV5L011, VNV5L012 and VNV5L013, as well as a comparison with release results of the marketed 2010/2011 season lot VNV5K002. Furthermore, also detailed information was provided on the manufacturing process parameters of multiple final container lots and intermediates (including VNV5L010, VNV5L011, VNV5L012 and VNV5L013). Release test results and process parameter test results did not reveal any parameters out of specification (OOS) or out of trend (OOT).

Based on the analysis of findings from the MVDA, only 3 process parameters could be linked with the impacted lot VNV5L010 that showed increased AEs:

1. slower infection of cells resulting in lower residual trypsin activity due to increased trypsin inhibitor formation by active cells;
2. prolonged duration of virus propagation phase (to achieve a sufficiently high HA yield) which may have resulted in increased release of trypsin inhibitor;
3. virus propagation (of lot VNV5L010) contains the lowest trypsin concentration after 42 hrs. These findings are in agreement with the low residual trypsin activity in the final container of lot VNV5L010.

To further elucidate the role of the low residual trypsin activity, a root cause investigation was performed. The provided data suggest that the high density complex, which is present in the final vaccine lots and at least in part degradable by trypsin, may contribute to an increased reactogenicity. Thus, high trypsin levels lead to degradation of the high density complex. The high density complex is reduced in vaccine batches containing higher amounts of trypsin. In addition, based on the expectation that the B strain is the main cause for reactogenicity, it is expected that for the A strains the difference in the response to the individual fractions is lower than for the B strain. This has been demonstrated on the basis of PBMC (peripheral blood mononuclear cells) assay following comparison with the A strains and confirmation of the high response factor for the high density fraction.

Clarifications were also provided by the MAH with regards to data provided showing that egg-derived vaccines contain high protease activity..

The MAH considers that the high density complex of the B strain and, the residual trypsin activity may contribute to an increased reactogenicity. The CHMP is in agreement with the MAH's conclusions and therefore considered the below corrective actions appropriate to address the issues.

Corrective actions

The MAH focused on their corrective actions to remove the high density complex and to standardize and control the trypsin addition scheme during manufacturing

The MAH presented corrective actions to improve the manufacturing process and control in order to reduce the reactogenicity potential of the finished product:

1. An additional ultracentrifugation step in manufacturing process (for all three strains) was proposed by the MAH to remove the high density complex. This proposed additional step was agreed with the CHMP.
2. To achieve a defined target activity, the MAH proposed a standardization and control of the trypsin addition during the manufacturing process. The standardized trypsin addition and control are acceptable to the CHMP.
3. Finally the MAH proposed to introduce limits for content of high density complexThe CHMP is in agreement with the introduction of cut off values for the high density complex and requests the MAH to submit the appropriate variations as further definition of the limits for content of high density complex resulting from the evaluation are to be implemented.

The Committee considers that these corrective actions will ensure the quality of Preflucel from the manufacturing perspective and that the appropriate corrective and preventive measures need to be implemented.

Clinical aspects

The CHMP considers that batches manufactured according to the improved process should be tested against appropriate product specifications and additional immunogenicity tests before being released on the market: the CHMP is of the opinion that the clinical immunogenicity profile after implementation of the additional steps in the manufacturing process would be required to show equivalent immunogenicity to the immunogenicity profile shown in the clinical trials for the initial MAA, along with further safety data with the product manufactured with the updated process.

The MAH proposed a randomized, age-stratified, double blind, controlled phase 3 study comparing a Vero cell-derived trivalent seasonal influenza vaccine made by the modified manufacturing process with vaccine made by the current manufacturing process and a licensed trivalent influenza vaccine in healthy adults aged 18 years and older. The aim of this trial is to demonstrate:

1. The comparable immunogenicity between the modified improved process and the current manufacturing process in healthy subjects aged 18 years and older,
2. The lot consistency with the implementation of the proposed manufacturing change,
3. And the non-inferior safety profile relative to a licensed comparator egg-derived vaccine.

The duration of the proposed trial is approximately 2 months, with initiation and completion planned for 1Q2013 and Q1/Q2 2013, respectively.

The CHMP is in agreement with the proposed protocol overall with the exception that the CHMP is of the opinion that the trial should be set up as an equivalence trial for the assessment of immunogenicity (and not as a non-inferiority study as proposed by the MAH).

The CHMP requests the MAH to submit a revised risk management plan once results of the immunogenicity testing become available for agreement with the National Competent Authorities.

In addition, the CHMP considers that a non-interventional PASS to further collect safety data following the improvement of the manufacturing process, with a specific focus on all hypersensitivity reactions (including anaphylactic reactions) should be performed. The protocol and milestones for this PASS should be provided by 2Q2013; this needs to be reflected in the updated risk management plan.

Finally the CHMP also considers that the risk management plan should be amended, in particular to include a close monitoring of ADR reporting rates focusing on reports of hypersensitivity, monthly ADR reporting rates focusing in particular on the incidence of all hypersensitivity reactions, a comparison of monthly reporting rates vs. 2011/12 and a separate evaluation of hypersensitivity and anaphylactic reactions in PSURs.

Overall conclusion

The root cause investigation was appropriately performed by the MAH. This investigation supports the conclusion that the high density complex, the residual trypsin activity and the B strain are the contributing factors to an increased reactogenicity.

The CHMP considers the below corrective actions that are to be implemented by the MAH through the appropriate variation application are appropriate to address the issues:

1. An additional ultracentrifugation step in the manufacturing process (for all three strains) to remove the high density complex;
2. a standardization and control of the trypsin addition scheme during the manufacturing process to achieve a defined target activity;
3. the introduction of limits for content of high density complex;
4. The inclusion of an additional IPC to the routine manufacturing process.

The CHMP agreed with the overall proposal for the clinical comparability study to evaluate the impact of the manufacturing changes on the immunogenicity and safety profile of the product after implementation of the additional steps in the manufacturing process. The immunogenicity assessment should be performed in an equivalence design. The outcome of this study along with appropriate amendments to the product information and updated risk management plan should be submitted to the National Competent

Authorities upon availability of the final results before batches produced with the improved manufacturing process are being released on the market.

The CHMP requests the MAH to provide the protocol and milestones of a non-interventional post-authorisation safety study to further collect safety data following the improvement of the manufacturing process, with a specific focus on all hypersensitivity reactions (including anaphylactic reactions). In addition, the risk management plan should also be amended, in particular to reflect the following CHMP requirements:

1. a close monitoring of ADR reporting rates focusing on reports of hypersensitivity,
2. monthly ADR reporting rates focusing in particular on the incidence of all hypersensitivity reactions,
3. a comparison of monthly reporting rates vs. 2011/12,
4. and a separate evaluation of hypersensitivity and anaphylactic reactions in PSURs.

In view of the above, the CHMP considered the benefit risk balance of Preflucel medicinal product is positive under normal conditions of use and therefore has recommended the maintenance of the Marketing Authorisations subject to conditions.

Grounds for the maintenance of the Marketing Authorisations subject to conditions

Whereas

- The Committee considers the procedure under Article 36 of Directive 2001/83/EC for the Influenza purified antigen containing medicinal products, Preflucel and associated names (see Annex I).

- The Committee notes that all batches of the product have been voluntarily recalled from the European market and are no longer distributed. The Committee notes the particular nature of this product as any flu vaccine for which application for yearly strain changes need to be approved by the Competent Authority and batches need to be released by the Competent OMCL before being placed to the market.

- The Committee considered the overall root cause investigation report and the proposed protocol for a clinical study to show that the immunogenicity profile following the improved manufacture of Preflucel and associated names is still comparable to the immunogenicity profile shown in the clinical trials for the initial MAA.
- The Committee concludes that a comprehensive investigation of the root cause within the licensed manufacturing process leading to the increased risk of hypersensitivity in subjects treated with Preflucel under normal conditions of use has been performed and considered all potential risk factors that could be identified. This investigation supports the reasoning that the high density complex associated with the B strain and the residual trypsin activity are the contributors to the increased reactogenicity.
- The Committee considers that several critical process steps and parameters were identified in the current manufacturing process and the appropriate corrective and preventive measures need to be implemented. In this regards, the Committee notes that an additional ultracentrifugation step in the manufacturing process (for all three strains) should be ensured, a standardization and control of the trypsin addition scheme during the virus propagation step should be applied, limits for content of high density complex should be introduced as well as an additional in process control (IPC) In that respect, a variation to the terms of the marketing authorisations concerning the required changes to the manufacturing process should be submitted.
- The Committee is of the opinion that results of additional immunogenicity tests should be submitted to the National Competent Authorities before batches are being released on the market. In addition, a protocol for a non-interventional post-authorisation safety study (PASS) to further collect safety data following the improvement of the manufacturing process, with a specific focus also on all hypersensitivity reactions (including anaphylactic reactions) should be provided; this needs to be reflected in the updated risk management plan.

- Finally, the MAH should submit a revised risk management plan for Preflucel and associated names before batches are being released on the market; the revised RMP should include a close monitoring and monthly ADR reporting rates focusing in particular on the incidence of all hypersensitivity reactions; a comparison of monthly reporting rates vs. the 2011/12 season and a separate evaluation of hypersensitivity ADRs (including anaphylactic reactions) in PSURs should also be reflected in the required amended RMP.

In view of the above, the Committee considers the benefit risk balance of Preflucel and associated names is positive under normal conditions of use and therefore recommends the maintenance of the marketing

authorisations with a variation to the marketing authorisations subject to the conditions set out in annex III for Preflucel and associated names (see Annex I).

Annex III

Conditions to the marketing authorisation

Conditions to the marketing authorisation

The National Competent Authorities coordinated by the Reference Member State, shall ensure that the following conditions are fulfilled by the MAH.

The below conditions should be fulfilled **before batches are being released on the market**:

QUALITY

1. A variation to the terms of the marketing authorisations concerning the changes to the manufacturing process as identified during the assessment should be submitted by the MAH.

CLINICAL

2. Results of additional immunogenicity tests should be submitted before batches are being released on the market.

   The required additional immunogenicity tests should show that the clinical immunogenicity profile after implementation of the additional steps in the manufacturing process is still comparable to the immunogenicity profile shown in the clinical trials for the initial MAA; safety data for the product manufactured with the updated process should also be provided.

   Submission of a revised risk management plan once results of the immunogenicity testing become available should be considered and agreed with the National Competent Authorities accordingly.

3. In addition, the Committee requires the MAH(s) to provide National Competent Authorities with interim results of the above-mentioned non-interventional PASS after release of the batches on the market.

PHARMACOVIGILANCE

4. a protocol and milestones for a non-interventional PASS to further collect safety data following the improvement of the manufacturing process, with a specific focus also on all hypersensitivity reactions (including anaphylactic reactions) should be provided by 2Q2013; this needs to be reflected in the updated risk management plan

5. The MAH is requested to submit a revised RMP to the NCAs. The RMP should be amended, in particular to include the following:
   a. a close monitoring of ADR reporting rates focusing on reports of hypersensitivity reactions;
   b. monthly ADR reporting rates focusing in particular on the incidence of all hypersensitivity reactions ;
   c. a comparison of monthly reporting rates vs. 2011/12;
   d. a separate evaluation of hypersensitivity ADRs (including anaphylactic reactions) in PSURs.

The below conditions should be fulfilled **following the release of batches produced according to the revised manufacturing process:**

PHARMACOVIGILANCE

6. Results/interim results of the non-interventional PASS in order to achieve further evidence on the safety of the product should be submitted in accordance with the agreed milestones (see condition 4).

7. The RMP should be updated to reflect the results of the non-interventional study.