COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Batrevac Tetra suspension for injection in pre-filled syringe 0.5 ml

Influenza virus surface antigens (inactivated) (haemagglutinin and neuraminidase)

NL/H/3845/001/DC

Date: 14 Augustus 2018

This module reflects the scientific discussion for the approval of Batrevac Tetra suspension for injection in pre-filled syringe 0.5 ml. The procedure was finalised on 10 July 2017. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMI	Cell Mediated Immunity
CMS	Concerned Member State
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
GMFI	Geometric Mean Fold Increases (GMFI)
GMT	Geometric Mean Titers (GMTs)
HA	Haemagglutinin
HI	Haemagglutination Inhibition
ICH	International Conference of Harmonisation
IgG	Anti-haemagglutinin Immunoglobulin G
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board
Ph.Eur.	European Pharmacopoeia
PIP	Paediatric Investigational Plan
PL	Package Leaflet
QBV	Quadrivalent Bulk Vaccine
QIV	Quadrivalent Influenza Vaccine
RH	Relative Humidity
RMP	Risk Management Plan
SAE	Serious Adverse Events
SmPC	Summary of Product Characteristics
TEAE	Treatment Emergent Adverse Events
TIV	Trivalent Influenza Vaccine
TIV(Vic)	B-strain of the Victoria lineage
TIV(Yam)	B-strain of the Yamagata lineage
TSE	Transmissible Spongiform Encephalopathy
VN	Virus Neutralisation

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Batrevac Tetra suspension for injection in pre-filled syringe 0.5 ml from Mylan Healthcare B.V.

The product is indicated for prophylaxis of influenza, especially in those who run an increased risk of associated complications.
Batrevac Tetra is indicated in adults (18 years of age and older). The use of this product should be based on official recommendations.

A comprehensive description of the indications and posology is given in the SmPC.

Influvac has been registered as a trivalent subunit influenza vaccine (TIV) since 1982, containing two A and one B-influenza strains. In 1992, the concentration of haemagglutinin (HA) per strain changed from 10 µg to 15 µg per strain in a standard dose of 0.5 ml. From 2004, the mercury-based preservative thiomersal has been removed from the commercial production process following a recommendation from the authorities.
Based on viral surveillance data, an influenza B virus representing one of these two lineages is selected each year to be included in the annual vaccine. The cross-protection against infection with one B lineage provided by immunisation with a vaccine derived from the other B lineage is uncertain but expected to be low. Predicting which lineage will predominate has been challenging, and in some seasons, there has been a mismatch between the lineage chosen for the vaccine and the predominant circulating influenza B virus lineage. Based on the demonstrated burden of influenza B, the limited cross-protection between the two influenza B lineages, and the inability to accurately predict which influenza B lineage will circulate, it may be expected that seasonal influenza vaccines will be improved by the inclusion of influenza B strains from both lineages.
In view of the above, the MAH of Influvac developed a quadrivalent influenza vaccine (QIV) to provide additional immunisation for the second recommended B strain.

This decentralised procedure concerns a so-called full dossier application according to Article 8(3) of Directive 2001/83/EC, a dossier with administrative, chemical-pharmaceutical, non-clinical and clinical data. The active component of Batrevac Tetra, suspension for injection 0.5 ml is considered to be well-known and the clinical pharmacology of influenza virus surface antigens inactivated (haemagglutinin and neuraminidase) has been extensively studied. Most of the data in the dossier of Batrevac Tetra, suspension for injection 0.5 ml was already submitted in the dossier of Influvac, (NL License RVG 22289).

The concerned member states (CMS) involved in this procedure were Austria, Germany and the United Kingdom.

Paediatric development
A paediatric investigational plan (PIP) has been developed and agreed by the Paediatric Committee of the European Medicines Agency (EMEA-001782-PIP01-15). A deferral and a waiver have been granted in accordance with Regulation (EC) No 1901/2006 (P/0182/2015). The waiver applies to infants of less than 6 months on the grounds that the specific medicinal product is likely to be ineffective.

Scientific advice
The MAH has sought national scientific advice on quality, toxico-pharmacological and clinical matters with Medicines Evaluation Board (MEB) in July 2013. In addition, the MAH received formal scientific advice given by both the European Medicines Agency (EMA) in October 2013 and the Dutch MEB (November 2013).

II. QUALITY ASPECTS

II.1 Introduction

Batrevac Tetra is a colourless clear liquid suspension for injection. The product contains the influenza virus surface antigens (haemagglutinin and neuraminidase) of the following strains:

- A/California/7/2009 (H1N1)pdm09-like strain (A/California/7/2009, X-181) — 15 micrograms HA
- A/Texas/50/2012 (H3N2)-like strain (A/Texas/50/2012, X-223A) — 15 micrograms HA
- B/Massachusetts/2/2012-like strain (B/Massachusetts/2/2012, BX-51B) — 15 micrograms HA
- B/Brisbane/60/2008-like strain (B/Brisbane/60/2008, wild type) — 15 micrograms HA

0.5 ml of the vaccine suspension for injection contains 15 micrograms of the antigen haemagglutinin of each recommended virus strain.

The virus strain composition is according to the recommendations by WHO and EMA for the season 2014 / 2015 NH.

The suspension for injection is packed in a pre-filled syringe (glass type 1) with or without needle.

The excipients are: potassium chloride, potassium dihydrogen phosphate, disodium phosphate dihydrate, sodium chloride, calcium chloride dihydrate, magnesium chloride hexahydrate and water for injections.

II.2 Drug Substance

Overall, the chemical-pharmaceutical documentation and quality overall summary in relation to the quadrivalent influenza vaccine (QIV) Batrevac Tetra are of sufficient quality in view of the present European regulatory requirements. The QIV documentation is generally acceptable for its scientific contents. The MAH confirmed that for all concerned test methods an assessment, and where necessary repeated validation, was conducted in the past 6 years. For all concerned test methods, the conclusions of the initial validation were fully confirmed. In view of this conclusion, the MAH is of the opinion that the validation reports from the trivalent influenza vaccine (TIV) dossier would still be applicable..

The information about the starting materials, description and control strategy of the drug substance is considered generally acceptable. This information is basically the same as for the approved TIV core dossier, but information is provided for the virus strains used in the 2014/2015 season, including information about the second B-strain. As per request, additional information has been presented about the haemagglutination inhibition (HI) assay applied to qualify the seed virus preparations. It is noted that the data requirements for HI-testing and their interpretation is currently discussed at the EU level.

Stability of drug substance

Stability studies have been performed with the drug substance. The proposed retest period for Monovalent Bulks is fifteen months but may be reduced if the stability studies suggest that a particular strain is less stable and some strains may not be stored for use during a subsequent season. Although re-testing is normally not accepted for biological substances, this is general practice for influenza monovalent bulk vaccine production/storage.

II.3 Medicinal Product

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. For the formulation of QIV one additional B-strain is added to the TIV formulation. The auxiliary/excipients components remain the same. The impact of the introduction of a second B-strain on the vaccine quality attributes has been investigated. The presented data do not indicate a major difference (if any) in the higher order (particle) structures present in QIV when compared to TIV.

Manufacturing process
The QIV manufacturing process and its control strategy are considered acceptable. As per request, further details have been provided on the drug product manufacturing process such as the intended manufacturing scale and the MAH's approach for assuring product sterility. It is stated that at the end of the filling process of each batch of the quadrivalent bulk vaccine (QBV), the sterility of the QBV is confirmed with a sterility test on a sample taken from the transfer set, between the aseptic connection and the sterilising filter. The measures taken to assure microbial quality of the final vaccine is deemed sufficient. At the end of the filling process of each batch of QBV, the sterility of the QBV is confirmed with a sterility test on a sample taken from the transfer set, between the aseptic connection and the sterilising filter.

Control of excipients
The excipients are purchased to the Ph. Eur. specifications. A test certificate guaranteeing compliance with the specifications accompanies each batch supplied. The specifications are acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for characteristics, identification, purity, content, pH and microbial purity. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. The MAH has sufficiently justified why the limits for total protein as stated in the Ph.Eur. monograph are not applicable for the product and adapted limits can be based taking into account the additional fourth strain. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from 4 batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for drug product are adequately described. The proposed shelf-life is 1 year when stored at +2°C to +8°C, in the original undamaged packaging and protected from direct sunlight for the drug product is considered acceptable. The stability profile of the QIV vaccine is comparable to that of the TIV. Therefore, the approved shelf life for TIV, i.e. 1 year when stored in a refrigerator (+2°C to +8°C) in the original package, can also be approved for the QIV.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Batrevac Tetra has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Introduction

For the pharmacodynamics characteristics of the proposed quadrivalent seasonal influenza vaccine formulation, reference is made to study results obtained with the authorised trivalent seasonal influenza vaccine Influvac, as well as to results from a study in which a monovalent seasonal influenza vaccine strain(A/New Caledonia/20/99 (H1N1)) was used as a reference. In addition, no new pharmacokinetic and toxicology data have been submitted as reference was made to Influvac.

III.2 Pharmacology

In the first study, guinea pigs following I.M. dosing of the full human dose (15 µg HA) of Influvac composition Northern Hemisphere season 2007/2008 or season 2008/2009 showed induction of antibodies against each of the six influenza virus strains. Titers increased until 21 days post dose, reaching a plateau thereafter.
In the second study in mice, immunogenic response against three batches of the virosomal influenza vaccine compared to trivalent subunit influenza vaccine Influvac, as well as a comparator virosomal vaccine (Inflexal) was evaluated. Immunogenic responses were comparable.
In the third study, the heterologous primed ferret was used as animal model for a sub-optimal dose determination using a monovalent seasonal (inactivated sub-unit) influenza vaccine, containing the A/New Caledonia/20/99 (H1N1) – virus strain, which was performed within the context of the development of a pandemic influenza vaccine (eventually adjuvanted). No unexpected effects of the test articles were observed in the ferret animal model. The results obtained are also thought to be supportive for a trivalent or quadrivalent seasonal influenza vaccine, also because the investigated strain is still part of the virus strain composition of current trivalent seasonal influenza vaccines, according to recommendations by WHO.
The immunogenic properties of influenza virus subunit vaccines have been described by Webster and Laver (1966), these study findings confirm the immunogenic properties of influenza virus antigens in a subunit influenza vaccine type, such as the now proposed quadrivalent influenza vaccine. Although in the current vaccine manufacturing process ether or sodium deoxycholate are no longer used. Webster and Askonas (1980) did report that seasonal inactivated influenza vaccines elicit anti-haemagglutinin Immunoglobulin G (IgG) antibodies directed against HA preventing cell infection, viral replication and disease could be attributed to the current proposed quadrivalent influenza vaccine. To a lesser extent, antibodies against NA and specific cytotoxic T-cells may also contribute to protection.

III.3 Pharmacokinetics

The absence of any pharmacokinetic studies is agreed for this quadrivalent influenza vaccine also in the light of the EU guideline on Influenza Vaccines (EMA/CHMP/VWP/457259/2014).

III.4 Toxicology

Single dose toxicity tests were performed where mice and guinea pigs were intraperitoneally injected with (trivalent) final bulk or vaccine lot. It did not result in death or illness. This showed absence of risk on abnormal toxicity for trivalent final bulks or vaccine final lots that can also be attributed to the proposed quadrivalent Influenza vaccine.

A repeated dose study in rabbits with the seasonal trivalent cell-derived influenza vaccine is regarded supportive for the proposed quadrivalent Influenza vaccine. General conclusion of this study is that the seasonal influenza vaccine used in this study did not show any systemic toxicity, unusual or unexpected results. Local mild inflammatory changes were present from day 3 onwards after vaccination, but reduction of inflammation was seen 28 days after inoculation in the non-adjuvanted influenza group.

The absence of genotoxicity studies is agreed and in accordance to the EU Guideline on Influenza Vaccines: Non-clinical and Clinical Module EMA/CHMP/VWP/457259/2014.

The absence of carcinogenicity studies is agreed since the proposed quadrivalent vaccine has no adjuvants and the formulation is similar to the current trivalent vaccine. It is also in accordance to the EU Guideline on Influenza Vaccines: Non-clinical and Clinical Module EMA/CHMP/VWP/457259/2014. Reproductive and developmental toxicity was investigated in rat using trivalent seasonal vaccine. No unusual results were obtained, and the safety of the vaccine in this respect was confirmed. Given the similarity of the quadrivalent vaccine with the trivalent (or monovalent) vaccine that was used for these studies, it is considered justified to extrapolate the results from the trivalent to the quadrivalent vaccine. Moreover, sufficient human data are present.

III.5 Ecotoxicity/environmental risk assessment (ERA)

The absence of an Environmental Risk Assessment is agreed as it is unlikely that the used influenza strains will result in any significant risk to the environment. The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, quadrivalent influenza vaccine is not expected to pose a risk to the environment.

III.6 Discussion on the non-clinical aspects

It is concluded that the submitted studies and literature deliver proof for the immunogenicity profile or the primary pharmacodynamics characteristics of the proposed quadrivalent influenza vaccine. The absence of pharmacokinetics studies and ERA is justified. The data summarised regarding the toxicology are acceptable. The overall non-clinical development was considered adequate the support the marketing authorisation for this product.

IV. CLINICAL ASPECTS

IV.1 Introduction

The clinical development program consists of a pivotal clinical phase III study in adults (study INFQ3001) to confirm comparability of the immunogenicity of the shared influenza strains contained in both the QIV and TIV formulations and comparability of the overall safety profile of QIV and TIV.
In addition, the MAH submitted 16 supportive TIV studies with the thiomersal-free formulation as supportive for the QIV to bridge the safety data between TIV and QIV.

IV.2 Pharmacokinetics

Pharmacokinetic studies were not performed, as they are not considered applicable. This is in accordance with the note for guidance on clinical evaluation of vaccines (CPMP/EWP/463/97).

IV.3 Pharmacodynamics

Mechanism of action
The principal objective of influenza vaccination is to protect the vaccinated, by active immunisation, from infection and disease caused by influenza viruses seasonally circulating in the population.
The most relevant immune response consists of the production of sufficient amounts of anti-haemagglutinin IgG antibodies. These antibodies bind to influenza viruses invading the respiratory tract and neutralize them before the viruses reach the cells of the respiratory epithelium (which are the primary host for viral replication) thus preventing cell infection, viral replication and disease. To a lesser extent, antibodies against neuraminidase and specific cytotoxic T-cells may also contribute to protection, particularly in subjects who do -for whatever reason- not produce sufficient antihaemagglutinin antibodies.
The results with regard to antibodies are described in the clinical efficacy section.

IV.4 Clinical efficacy

The main study is study INFQ3001. This phase III study was conducted in 1980 adults and elderly to evaluate comparability of the immunogenicity of the shared influenza strains contained in both the QIV and TIV formulations and comparability of the overall safety profile of QIV and TIV.

Study INFQ3001 was a randomised, double-blind, active-controlled immunogenicity study stratified 1:1 for age into adults (≥ 18 to ≤ 60 years) and elderly (≥ 61 years) cohorts.

Participants
Men and women aged ≥ 18 years of age at the day of study vaccination in stable health. Subjects belonging to risk groups for influenza for which there is a general consensus across European Union Countries for vaccination priority groups were enrolled.

Primary objective
The primary objectivity of the study was to demonstrate the non-inferiority of QIV, with respect to postvaccination geometric mean HI antibody titers against the shared strains, compared with the TIVs with either the B-strain of the Victoria lineage (TIV(Vic)) or the B-strain of the Yamagata lineage (TIV(Yam)).
Virus neutralisation (VN) and cell mediated immunity (CMI) were secondary outcomes.

Treatments
The active drug substance consisted of 15 µg of HA of each of the three or four viral strains recommended by the WHO and CHMP for the 2014/2015 season in the Northern Hemisphere.

The strains of the QIV were:
- A/California/7/2009 (H1N1)pdm09-like strain (A/California/7/2009, X-181)
- A/Texas/50/2012 (H3N2)-like strain (A/Texas/50/2012, X-223A)
- B/Massachusetts/2/2012-like strain (B/Massachusetts/2/2012, BX-51B)
- B/Brisbane/60/2008 (wild type)

The strains of the TIV(Vic) were the same A strains as in the QIV and B/Brisbane/60/2008 (wild type).
The strains of the TIV(Yam) were the same A strains as in the QIV and B/Massachusetts/2/2012-like strain (B/Massachusetts/2/2012, BX-51B). Each subject received one dose (0.5 mL) of influenza vaccine by intramuscular injection in the deltoid muscle of the upper arm.

Statistical methods
The planned number of subjects was a total of 1,980: 1,540 QIV:220 TIV(Vic):220 TIV(Yam). This would result in an overall statistical power of > 95% to demonstrate the non-inferiority of QIV to TIV with respect to immunogenicity against the shared strains. The non-inferiority margin was set at 1.5.
HI titre was the primary outcome, measured at day 1 and day 22.

Results
The study was conducted in 1,980 randomised subjects: 1,535 subjects received the QIV: 768 adults (≥ 18 to ≤ 60 years of age) and 767 elderly (≥61 years of age), and 442 subjects received a TIV (222 adults and 220 elderly).
The majority of subjects were white (99.5%). A total of 859 subjects (43.4%) were males and 1,121 subjects (56.6%) were females. The mean (SD) age at screening was 55.7 (17.7) years. Percentages of subjects at risk for influenza were 13.8% and 9.5% in adults and 45.2% and 40.2% elderly for the QIV and TIV, respectively – representative for those targeted within influenza vaccination programs.

Primary efficacy
The non-inferiority of QIV to TIV with respect to the induced immunogenicity against the shared strains was tested by comparing the postvaccination geometric means of the HI titers against these strains between the quadrivalent formulation and the trivalent formulations (see table below).

Table 1: Non-inferiority of QIV versus TIV against shared strains based on post vaccination geometric mean HI titers - Per-Protocol Sample – Study INFQ3001

Strain	QIV[1]		TIV[a]		TIV[a]/QIV
	N	GMT	N	GMT	Adjusted GMR (95% CI)
A(H1N1)	1511	186.6	433	220.9	1.18 (1.023, 1.370)
A(H3N2)	1524	393.1	436	413.5	1.06 (0.928, 1.213)
		QIV		$TIV_{(Vic)}$	$TIV_{(Vic)}$/QIV
B-Victoria	1521	152.9	215	142.0	0.88 (0.726, 1.071)
		QIV		$TIV_{(Yam)}$	$TIV_{(Yam)}$/QIV
B-Yamagata	1520	102.1	215	86.1	0.82 (0.677, 0.998)

[1] [a] HI titer data of the two trivalent formulations were pooled for the two A-strains.

For all four strains, the upper limit of the 95% confidence interval for the geometric mean ratio (GMR; TIV versus QIV) fell below the predefined non-inferiority margin of 1.5, meaning that the non-inferiority of QIV to TIV was demonstrated. The pre- and post-vaccination geometric mean titres (GMTs) for HI by age group were comparable between QIV and TIV.

Secondary efficacy
The immune response measured by HI was superior for each of the B-strains in the QIV when compared to the TIVs with the alternate B-strain. Geometric mean fold increases (GMFI) were similar across vaccination groups for all strains. In the adult subjects, the GMFIs varied between 6.3 and 11.4 in the QIV group and between 6.2 and 11.7 in the TIV groups (excluding alternate lineages). In the elderly subjects, the GMFIs varied between 4.2 and 5.5 in the QIV group and between 2.1 and 6.9 in the TIV groups (excluding alternate lineages).Seroconversion rates were comparable between vaccination groups but lower in the TIV group for the not-included B-strain due to limited cross-reactivity. Responses in elderly in both groups were lower than in adults.

CMI
The numbers of subjects in which cell mediated immunity analyses were reported, were very low varying from 3-18 subjects. The CMI response is lower in the elderly population than in adults. However, it should be noted that as data are very limited no firm conclusions can be drawn.

Conclusion on clinical efficacy
- The immune response measured by HI induced by the QIV was non-inferior to that induced by the TIV for the corresponding influenza strains.
- The immune response measured by HI was superior for each of the B-strains in the QIV when compared to the TIVs with the alternate B-strain.
- Overall the immune response in the elderly population was lower compared to the adult population.
- Virus neutralisation data were in line with the HI data.
- CMI data are too limited to draw firm conclusions.
- The immune response measured by GMT does not seem to be influenced by the at risk status of the subjects, this accounts for adults as well as for elderly

IV.5 Clinical safety

Safety findings of pivotal study INFQ3001 and the overall safety findings of the clinical data base of the TIV in which the data of 16 supportive studies are compiled. The supportive studies are 11 annual update studies and 5 comparative studies.

Solicited adverse events within 7 days after vaccination
Local reactions
In both adults and elderly the reporting rates of local reactions were generally low (respectively <10% and <5%). In adults, except for vaccination site pain, reporting rates of all other local reactions were slightly lower in the QIV group than in the TIV group. The reporting rates were slightly higher in the QIV group than the TIV group in elderly. None of these differences reached statistical significance and thus were not flagged as a potential safety issue.

The percentage of subject's local reactions in study INFQ3001 is in line with those found in the clinical database

Systemic reactions
For both adults and elderly, headache and fatigue/tiredness were the most frequent systemic reactions within 7 days after vaccination in both vaccination groups. Most of the systemic reactions were mild or moderate in severity. The differences in rates between QIV and TIV were relatively small, although only one reaction (arthralgia/joint pain, 5.8% [QIV] versus 2.3% [TIV]) reached statistical significance in elderly, thus was flagged as having a potentially higher reporting rate for elderly subjects in the QIV group. Overall, all systemic reaction symptoms lasted for 1 to 3 days for the majority of subjects in both vaccination groups.
The percentage of subjects with systemic reactions in study INFQ3001 is in line with those found in the clinical database.

Unsolicited adverse events between day 1 and day 22
The proportion of adults and elderly subjects with study vaccine-related treatment emergent adverse events (TEAEs) were respectively 0.6% and 0.8% across vaccination groups. Only the TEAE preferred term asthenia was reported in more than 1 subject from the adult group (2 subjects (0.3%) in the QIV group). In the clinical study database the most frequently reported TEAEs were nasal congestion (0.7% of the adults and 0.1% of the elderly adults) and oropharyngeal pain (0.6% and 0.1%, respectively), followed by cough (0.3% and 0.2%, respectively), nasopharyngitis (0.3% and 0.1%, respectively), pain and headache (both 0.2% in adults only). All other treatment-related adverse events were reported by 0.1% of the subjects.

Serious adverse events/deaths
Up to day 22 there were no serious adverse events (SAEs) that were considered to have reasonable possibility for casual relationship with the vaccine. No SAEs reported from day 22 up to month 6 in both the study as well as the clinical database were considered to have a reasonable possibility for casual relationship with the vaccine.

Discontinuation due to adverse events
No adult or elderly subjects discontinued the study up to day 22. Three elderly adults discontinued treatment due to a SAE (confusional state, ductal adenocarcinoma of pancreas, and coronary artery disease). Each of these adverse events was considered to be not related to the vaccination.

IV.6 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Batrevac Tetra.

Important identified risks	• Hypersensitivity to the active substances or to any of the excipients
Important potential risks	• Non-febrile convulsions • Adverse events following immunisation of possible autoimmune nature (e.g. Guillain-Barré syndrome, neuritis, encephalomyelitis, demyelinating disease, vasculitis, thrombocytopenia) • Vaccination failure
Missing information	• Safety in immunocompromised patients

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.7 Discussion on the clinical aspects

Influvac has been registered as a trivalent influenza vaccine since 1982 with two A-strains and one B-strain. In order to broaden the protection, the MAH developed a quadrivalent influenza vaccine, Batrevac Tetra, with two A and two B strains. A clinical study showed that that the HI immune response for all four strains induced by the QIV was non-inferior to the immune response induced by the TIV with corresponding strains. No new safety signals were seen in this study. The overall safety profile based on local and systemic reactions and long term data up to 6 months after vaccination of the QIV was comparable to that of the TIV. In addition, the found safety profile of the QIV is in line with what was found in previous TIV studies.

V. USER CONSULTATION

The applicant submitted a statement on Readability User Test that the proposed common Package Leaflet (PL) for quadrivalent influenza vaccine Batrevac Tetra (surface antigen, inactivated) is comparable with the current common PL for trivalent influenza vaccine Influvac (surface antigen, inactivated). The MAH confirmed that both PLs are comparable regarding lay-out. The font size and headings will be identical for both PLs. It was concluded that it is justified that a specific Readability User Test will not be necessary for the proposed PL for Batrevac Tetra.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Influvac has been registered as a trivalent influenza vaccine since 1982 containing two A-strains, currently A/H1N1 and A/H3N2, and one B-strain. Batrevac Tetra was developed to address a potential risk of sub-optimal protection of the TIV against circulating B lineages due to risk on mismatch between the B strain recommended for inclusion in the trivalent influenza vaccines and the dominant circulating B strain.

The chemical-pharmaceutical information about the manufacturing, the quality requirements with regard to Batrevac Tetra, suspension for injection in a prefilled syringe, has a proven chemical-pharmaceutical quality.

The non-clinical data documentation provided did not give rise to specific concerns for humans that would preclude a recommendation for marketing authorisation.

The efficacy of the QIV is inferred from the demonstration of non-inferior immune response of the Batrevac Tetra compared with Influvac. Per guideline on influenza vaccines (EMA/CHMP/VWP/457259/2014), authorisation of new inactivated non-adjuvanted seasonal influenza vaccines manufactured and containing a final HA content similar to that of an EU-authorised inactivated non-adjuvanted vaccine may be based on comparative safety and immunogenicity studies. Despite the lack of a confirmed immunological correlate of protection, demonstration of immunological non-inferiority of the candidate vaccine versus comparator vaccine is considered to reflect at least comparable protective efficacy. Programs are implemented to estimate the effectiveness post-marketing depending on the extent of use of Batrevac Tetra.

The pivotal study, INFQ3001, was developed according to the CHMP guidelines and Scientific Advice from the CHMP and MEB. The study was conducted in adults (≥ 18 to ≤ 60 years of age) and elderly (≥61 years of age), with a sufficient amount of subjects belonging to the risk groups for influenza. The study was powered to evaluate non-inferiority of the immune response induced by the QIV compared to that of the TIV for the combined population adults and elderly.

The results of the pivotal clinical study INFQ3001 showed non-inferiority of the immune response induced by the quadrivalent influenza vaccine compared to that of the trivalent influenza vaccine for the combined population adults and elderly and a comparable safety profile.

It can be concluded that the increasing antigen amount due to the additional B strain does not have any clinically relevant impact on the safety of the vaccine. The safety profile of QIV is considered positive.

In a meeting on 7 December 2016, the Board decided that the efficacy of the product is established.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that Batrevac Tetra demonstrated adequate evidence of efficacy in the indication applied for. The decentralised procedure was finalised with a positive outcome on 10 July 2017.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
NL/H/3844/001/WS/001	Changes in the manufacturing process of the active substance; the change refers to a biological / immunological substance or use of a different chemically derived substance in the manufacture of a biological/immunological substance, which may have a significant impact on the quality, safety and efficacy of the medicinal product and is not related to a protocol	-	25-01-2018	Approved	-
NL/H/3844/001/WS/002	Changes in the manufacturing process of the active substance; minor change in the manufacturing process of the active substance	-	12-01-2018	Approved	-
NL/H/3844/001/II/003	Changes to the active substance of a seasonal, pre-pandemic or pandemic vaccine against human influenza; replacement of the strain(s) in a seasonal, pre-pandemic or a pandemic vaccine against human influenza	-	12-02-2018	Approved	-
NL/H/3844/001/IA/005	Change in the name and/or address of the marketing authorisation holder	-	29-01-2018	Approved	-
NL/H/3844/001/II/006	Changes to the active substance of a seasonal, pre-pandemic or pandemic vaccine against human influenza; replacement of the strain(s) in a seasonal, pre-pandemic or a pandemic vaccine against human influenza	Y	25-07-2018	Approved	-