



Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for influenza virus haemagglutinin (vaccine)

Proprietary Product Name: Influvac Tetra

Sponsor: Mylan Health Pty Ltd

August 2018

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- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
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- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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Common abbreviations

Abbreviation	Meaning
ACIP	Advisory Committee on Immunization Practices (US)
ACV	Advisory Committee on Vaccines (TGA)
ASA	Australian Specific Annex
ASCIA	Australasian Society of Clinical Immunology and Allergy
CHMP	Committee for Medicinal Products for Human Use (EMA)
CPD	Certificated Product Details
DLP	Data lock point
DLS	Dynamic Light Scattering
EMA	European Medicines Agency
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration (US)
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GMR	Geometric mean ratio
GMT	Geometric mean titre
HA	Haemagglutinin
HI	Haemagglutination inhibition
ICH	International Conference on Harmonisation
IM	Intramuscular
IM	Intramuscular
MBV	Monovalent bulk vaccine
NA	Neuraminidase
Ph. Eur.	European Pharmacopoeia
PI	Product Information

Abbreviation	Meaning
PP	Per Protocol
PSUR	Periodic safety update report
PT	Preferred Term
QIV	Quadrivalent influenza vaccine
RMP	Risk Management Plan
SC	Subcutaneous
SOC	System Organ Class
TIV	Trivalent influenza vaccine
TIV _(Vic)	Trivalent influenza vaccine with influenza B(Victoria) strain
TIV _(Yam)	Trivalent influenza vaccine with influenza B(Yamagata) strain
US	United States (of America)
VN	Virus neutralisation
WHO	World Health Organization

I. Introduction to product submission

Submission details

<i>Type of submission:</i>	New chemical entity
<i>Decision:</i>	Approved
<i>Date of decision:</i>	1 November 2017
<i>Date of entry onto ARTG</i>	2 November 2017
<i>Active ingredient:</i>	Influenza virus haemagglutinin (vaccine)
<i>Product name:</i>	Influvac Tetra
<i>Sponsor's name and address:</i>	Mylan Health Pty Ltd 30-34 Hickson Road, Millers Point, NSW, 2000
<i>Dose form:</i>	Suspension for injection
<i>Strength:</i>	60 µg/0.5 mL
<i>Container:</i>	Pre-filled syringe without needle Pre-filled syringe with 16 mm needle Pre-filled syringe with 25 mm needle
<i>Pack sizes:</i>	1 x syringe pack; 10 x syringe pack
<i>Approved therapeutic use:</i>	<i>For the prevention of influenza caused by influenza virus, types A and B. For full details regarding recommendations for influenza vaccination, please refer to the relevant National Immunisation Guidelines. Influvac Tetra is indicated in adults (18 years of age and older).</i>
<i>Routes of administration:</i>	Intramuscular; subcutaneous
<i>Dosage:</i>	Seasonal (annual) vaccination; for full details regarding recommendations for influenza vaccination, please refer to the relevant National Immunisation Guidelines and the Product Information (PI).
<i>ARTG numbers:</i>	281035: Pre-filled syringe without needle 292237: Pre-filled syringe with 16 mm needle 292238: Pre-filled syringe with 25 mm needle

Product background

This AusPAR describes the application by the sponsor to register Influvac Tetra influenza virus haemagglutinin 0.5 mL vaccine in the dosage forms of prefilled syringe without needle, with 16 mm needle, and with 25 mm needle for the following indication:

'For the prevention of influenza caused by influenza virus, types A and B'.

The rationale for quadrivalent influenza vaccines (QIV) is that two antigenically distinct lineages of influenza B viruses have circulated globally since 1985. However, until 2012 licensed trivalent (seasonal) influenza vaccines (TIV) contain antigens from only a single influenza B virus and thus provide limited immunity against circulating influenza B strains of the lineage not present in the vaccine. Seasonal influenza vaccines could be improved by inclusion of influenza B strains of both lineages. Inactivated QIVs have been registered in Australia and include FluQuadri/FluQuadri (Sanofi Pasteur Australia Pty Ltd) Fluarix Tetra (GlaxoSmithKline Australia Pty Ltd) and Afluria Quad (Seqirus), all with various age-based indications.

In Australia, the inactivated TIV subunit vaccine Influvac was first registered in 2002 and Influvac Junior was registered in 2006. Influvac contains 15 µg haemagglutinin (HA) per strain. Extensive clinical experience gained with the TIV Influvac for over ≥ 30 years is considered relevant for the development of the quadrivalent vaccine as the antigens of the influenza strains in both formulations and manufacturing methods are the same.

The submitted dossier for this application includes one completed Phase III clinical study report in adults (Study INFQ3001). This study is one of three studies in the development program for Influvac Tetra that was conducted in accordance with European Union (EU) regulatory guidance

Regulatory status

Influvac (as a TIV) has been marketed as an inactivated surface antigen, subunit vaccine since 1982. It is registered in over 80 countries worldwide, including Australia. This submission represents a new and first application for Influvac Tetra, a QIV.

At the time the TGA considered this application, similar applications for the Influvac Tetra (QIV) were under consideration from 2016 onwards in the EU (under the decentralised procedure), Switzerland and New Zealand.

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>>.

II. Registration time line

The following table captures the key steps and dates for this application PM-2016-02725-1-2 and which are detailed and discussed in this AusPAR and Attachment 2.

Description	Date
Submission dossier accepted and first round evaluation commenced	30 November 2016
First round evaluation completed	4 May 2017
Sponsor provides responses on questions raised in first round evaluation	30 June 2017
Second round evaluation completed	23 August 2017

Description	Date
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	5 September 2017
Sponsor's pre-Advisory Committee response	19 September 2017
Advisory Committee meeting	4 October 2017
Registration decision (Outcome)	1 November 2017
Completion of administrative activities and registration on ARTG	2 November 2017
Number of working days from submission dossier acceptance to registration decision*	189

*Statutory time frame is 255 working days

III. Quality findings

Drug substance (active ingredient)

Structure

The drug substance structure is not provided in the dossier. It is presumed that the risks associated with the structure of new influenza virus subtype are covered by the existing registration of currently registered TIV product, Influvac.

Physical and chemical properties

According to the sponsor, the product is buffered to maintain its tonicity and pH. The presence of magnesium and calcium ions during processing and in the final lot improves the stability of the HA antigens.

The higher order (particle) structure (in which HA and neuraminidase (NA) antigens are organised) were characterised. The sponsor has provided information on the control strategy for aggregates which is based on the annual monovalent bulk vaccine (MBV) characterisation studies using dynamic light scattering profiling. Aggregates in MBV are considered as representative for the final lot. Storage up to 20 months did not change the aggregation profile. The sponsor has confirmed that annual strain update will include MBV characterisation reports (first 3 batches) for each new virus strain in the product. Additionally, the physiochemical characterisation of the QIV product (Influvac Tetra) is not expected to be different than TIV product (Influvac).

Overall, supplied data is satisfactory and there are no quality related concerns pertaining to this issue.

Drug product

The product could be supplied in 3 presentations: a syringe with 16 mm needle, a syringe with 25 mm needle and a syringe without needle. In this regard, the sponsor has

confirmed that for the Southern Hemisphere 2018 influenza season, the sponsor plans to supply Influvac Tetra with the 16 mm needle presentation only.

Good Manufacturing Practice (GMP) certification is current.

There are no issues pertaining to manufacture or manufacturer of the product. All analytical procedures are validated and there are no issues pertaining to specifications.

Stability

Stability data have been generated under stressed and real time conditions to characterise the stability profile of the product. Stability studies have been conducted in accordance with relevant International Conference on Harmonisation (ICH) guidelines.

There are no issues pertaining to stability of drug product. There are no objections to the registration of this product from sterility; endotoxin and container safety related aspects.

Overall, sufficient evidence has been provided to demonstrate that the risks related to the manufacturing quality of Influvac Tetra, inactivated QIV (surface antigen) have been controlled to an acceptable level.

Quality summary and conclusions

There are no further objections to the registration of Influvac Tetra, inactivated QIV (surface antigen).

Please note that a modified inactivation process is being evaluated in an independent submission for the trivalent (TIV) product Influvac. No data related to the modified inactivation process was supplied in the dossier for the Influvac Tetra submission. Therefore, this summary report and recommendations are not based on the modified inactivation process.

This summary report does not include the final position relating to viral safety. matters related to viral safety are to be finalised with the sponsor by the viral safety unit.

Please also note that the product could be supplied in three presentations: (1) syringe with 16 mm needle, (2) syringe with 25 mm needle and (3) syringe without needle. In this regard, the sponsor has confirmed that for the Southern Hemisphere 2018 season, the sponsor plans to supply Influvac Tetra with the 16 mm needle presentation only.

Proposed conditions of registration for the delegate

Batch release testing

It is a condition of registration that all independent batches of Influvac Tetra, Inactivated Quadrivalent Influenza Vaccine (surface antigen) imported into Australia are not released for sale until samples and the manufacturer's release data have been assessed and the sponsor have received notification acknowledging release from the Laboratories Branch, TGA.

For each independent batch of the product imported into Australia, the Sponsor must supply the following:

- A completed Request for Release Form.
- Complete summary protocols for manufacture and QC, including all steps in production.
- At least 20 packaged doses of each first consignment of product lot with the Australian approved labels, PI and packaging. 10 packaged doses of any further consignment of

already released product (including diluents) with the Australian approved labels, PI and packaging.

- Evidence that the consignment has been shipped under the approved storage conditions between the manufacturer and Australia.
- Certificate of Release from regulatory agency acting for the country of origin such as an OMCL (if available).
- Any reagents, reference material and standards required to undertake testing, as requested by Laboratories Branch, TGA.

Distribution of each shipment of each batch of vaccine is conditional upon fulfilment of these conditions and receipt of a letter from the Laboratories Branch acknowledging release.

Certified Product Details

An electronic copy of the Certified Product Details (CPD) should be provided upon registration of the therapeutic good. In addition, an updated CPD should be provided when any changes to finished product specifications and test methods are approved in a separate application or notified through a self-assessable change.

IV. Nonclinical findings

No studies were conducted with the quadrivalent vaccine. The reference member state (Netherlands) for the EU submission agreed that no new nonclinical studies were necessary, but requested that previously conducted studies with Influvac TIV and/or literature be submitted.

Nonclinical summary and conclusions

Summary

No nonclinical studies were conducted with the quadrivalent vaccine, previous studies with the Influvac TIV and some publications were submitted in response to a request by the reference member state for the EU application. The TIV was registered in Australia in 2002 without nonclinical data. The lack of new nonclinical studies with Influvac Tetra is consistent with European Medicines Agency (EMA) guidance for a new influenza vaccine based on an existing manufacturing process.¹

A single intramuscular (IM) dose of Influvac TIV induced specific Haemagglutination inhibition (HI) titres in guinea pigs by 22 days post-dose. A single intraperitoneal (IP) dose of Influvac TIV induced HI titres ≥ 40 in all mice.

A dose range (0.6 to 15 μg HA) study with monovalent A/New Caledonia/20/99 (H1N1) influenza vaccine in heterologously primed ferrets showed that the suboptimal dose, defined as the dose which induced an immune response, but still left enough room for optimisation of the response by addition of an adjuvant, after a single dose was 5 μg HA, and 1.7 μg HA per dose after 2 doses. There were no adverse effects.

Several papers/reviews, some of limited relevance, described various aspects of mechanisms of action of inactivated influenza vaccines.

¹ EMA (2016). Guideline on influenza vaccines. Nonclinical and clinical module. (EMA/CHMP/VWP/457259/2014).

All 197 trivalent final bulks and 572 vaccine lots of Influvac TIV manufactured between 1987 and 1995 passed abnormal toxicity testing (test no longer required).

A repeat-dose toxicity study in rabbits which included monovalent A/New Caledonia/20/99 (H1N1) inactivated influenza vaccine showed no systemic toxicity, and very slight to moderate microscopic inflammatory changes consisting of mixed or polymorphonuclear cell infiltrate from Day 3 post-dose onwards, which had partially recovered 28 days after vaccination.

A preliminary reproductive toxicity study in rats in which the human dose of trivalent influenza vaccine was administered IM 28 and 14 days prior to mating showed no adverse effects up to Gestation Day 20. Most rats developed an antibody response, and some antibody transfer to fetuses occurred.

Although limited, the nonclinical data raise no objections to registration of Influvac Tetra vaccine.

Conclusion and recommendation for the delegate

There are no nonclinical objections to registration of Influvac Tetra vaccine however evaluation of efficacy and safety will largely rely on clinical data.

V. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Clinical rationale

Each year in Australia influenza infection affects somewhere between 5 to 10% of the general population and this can be up to 20% in some years. Among Australian patients aged ≥ 50 years, influenza is annually associated with $> 3,000$ deaths and $> 13,500$ hospitalisations.² According to the World Health Organization (WHO), vaccination is the most effective way to prevent influenza and its complications.

Switch from trivalent to quadrivalent vaccine

The planned change from the TIV to the QIV is not associated with major changes in the general production process, and therefore no change in the safety profile is expected. Extensive clinical experience gained with Influvac (TIV) for over ≥ 30 years is considered relevant for the development of the QIV as the antigens of the influenza strains in both formulations are similar. In fact, both the Victoria and Yamagata B strain lineages, either one or the other, have been present in former Influvac (TIV) formulations and the immunogenicity and safety has been extensively studied in clinical studies. For the currently used thiomersal free trivalent formulation, the Yamagata lineage has been contained in the vaccine for 5 out of 10 seasons versus 5 seasons for the Victoria-lineage. The immunogenicity, safety and reactogenicity profiles were similar, therefore it is not expected that the combination of the 2 B strain lineages in the quadrivalent vaccine will result in a different immunogenicity and safety profile compared to the Influvac TIV. This view is strengthened by recent publications comparing the quadrivalent and trivalent

² Based on immunise.health.gov.au website data

formulations of other influenza vaccines.^{3,4,5,6,7,8} In these studies, reactogenicity and safety of the quadrivalent formulations was consistent with the established profiles of the corresponding trivalent formulations. In addition, the second B strain in the quadrivalent formulations did not impact immune responses elicited by the 3 strains contained in the trivalent formulations.

Contents of the clinical dossier

The submission contained the following clinical information:

- A Clinical Overview, Summary of Clinical Efficacy, Summary of Clinical Safety.
- A pivotal Phase III randomised, multicentre, double blinded study to evaluate the quadrivalent vaccine versus 2 TIVs each containing one of the 'B' strains contained in the QIV.

Paediatric data

The submission does not include paediatric efficacy/safety data, although paediatric studies are ongoing and/or planned. See Attachment 2 for details of ongoing or planned studies.

Good clinical practice

Approvals to undertake the clinical studies were obtained from appropriately constituted institutional ethics committees/independent research boards, in accordance with the relevant national guidelines and regulations applicable. The studies presented in this submission were conducted in accordance with Good Clinical Practice (GCP).

Pharmacokinetics

With respect to the nature of the product, clinical pharmacology data have not been assessed. The subunit influenza vaccine, as all vaccines, induces antibodies, which consecutively are responsible for the desired effect of the intervention, that is, protection against an infectious disease (principle of active vaccination). The constituents of the vaccine itself are phagocytosed at the site of injection. Therefore, specific interaction or pharmacokinetic studies have not been carried out in man.

Immunogenicity

Efficacy and safety data arising from the pivotal study (Study INFQ3001) is summarised in Sections 7 and 8 respectively of Attachment 2. A number of supportive immunogenicity

³ Greenberg D, et al. Safety and immunogenicity of a quadrivalent inactivated influenza vaccine compared to licensed trivalent inactivated influenza vaccines in adults. *Vaccine* 2013;31(5):770-6.

⁴ Greenberg D, et al. Safety and Immunogenicity of an Inactivated Quadrivalent Influenza Vaccine in Children 6 Months through 8 Years of Age. *Pediatr Infect Dis J*. 2014 Jan 17.

⁵ Jain V et al. Vaccine for prevention of mild and moderate-to-severe influenza in children. *N Engl J Med*. 2013; 369(26):2481-91

⁶ Domachowske J, et al. A Randomized Trial of Candidate Inactivated Quadrivalent Influenza Vaccine versus Trivalent Influenza Vaccines in Children Aged 3-17 Years. *J Infect Dis* 2013;207(12):1878-87.

⁷ Pépin S, et al. Safety and immunogenicity of a quadrivalent inactivated influenza vaccine in adults. *Vaccine*. 2013; 31(47):5572-8.

⁸ Langley J, et al. Immunogenicity and safety of an inactivated quadrivalent influenza vaccine candidate: a Phase III randomized controlled trial in children. *J Infect Dis*. 2013; 208(4):544-53.

studies have previously been reviewed by the TGA, and can be considered supportive of this submission.

Evaluator's conclusions on immunogenicity

None of the supportive immunogenicity studies provide any data for a QIV. All pertain to the immunogenicity and safety of TIVs containing 2 influenza A strains and 1 influenza B strain. Each vaccine contains 15 µg of HA per strain. These data are included because they show that the 'B' strain as a component of these trivalent vaccines were safe and immunogenic.

Dosage selection for the pivotal studies

The dosage selection for the addition B strain immunogen in Influvac Tetra was based upon the standard used in the TIV, that is, 15 µg of HA per strain.

Efficacy

Studies providing efficacy data

The pivotal Study INFQ3001 is not an 'efficacy' study, instead the immunogenicity data derived is used as a surrogate for clinical efficacy. This is a standard approach in influenza vaccine studies. The study was designed according to the Guideline on Clinical Evaluation of New Vaccines (EMA/CHMP/VWP/164653/2005) and the scientific advice from an EU national competent authority for registration of QIV in the adult/elderly population. Anti-HA antibody response is an established correlate of protection against influenza in adults; therefore, HI titre was the primary outcome measure in this study. The study aimed to demonstrate the comparability of the immunogenicity of the shared strains contained in both the QIV and TIV formulations. Therefore, the primary objective was to demonstrate that the post-vaccination HI antibody responses with QIV for each of the shared strains were non-inferior to those with the TIVs. The non-inferiority margin was set at 1.5, which was in agreement with the scientific advice obtained from an EU national competent authority and was also in accordance with the margin recommended by the United States (US) Food and Drug Administration (FDA) guidelines. As a secondary efficacy objective, the study aimed to demonstrate that the added B strain in QIV provided an antibody response superior to that with the TIV for the alternate B strain lineage. In addition, the immunogenicity of each of the strains in QIV and TIVs was further characterised by describing the derived serology parameters of seroconversion, and mean fold increase with respect to HI and virus neutralisation (VN) antibody titres and by performing analyses in study population subsets according to age and pre-existing antibody status. Furthermore, cell mediated immunity values were described for a subset of subjects, with the central laboratory performing the HI assays, in accordance with the guidelines indicated by EMA:

- Any HI result < 10 (= undetectable) was expressed as 5;
- Sera which have a titre ≥ 10 but < 40 are considered positive but not protective;
- Sera with a titre ≥ 40 are considered positive and protective.

Evaluator's conclusions on efficacy

Study INFQ3001 conducted entirely within the EU, demonstrates the immunogenicity of Influvac Tetra in adults aged 18 to 60 years and the elderly aged ≥ 61 years against all 4 strains of influenza virus contained within the vaccine. Standard methodology to

demonstrate immunogenicity was utilised. Importantly, the added B strain provides superior immunogenicity without affecting the antibody response to the other strains and there is no safety cost (discussed in under Safety, below). Seroprotection rates for all 4 strains in the QIV were higher in adults compared to the elderly, but nevertheless high in both groups. Lower seroprotection in the elderly is a universal finding in immunogenicity studies for influenza vaccines (that is, not a unique finding for this vaccine) and the reviewer has no concerns about this finding in the pivotal study and the pooled analyses.

Safety

Studies providing safety data

There is one key study, Study INFQ3001 described above, that provided evaluable safety data for the QIV.

Patient exposure

1535 adults received a single dose of the QIV. Of the 990 vaccinated adult subjects, 768 received a single vaccination of QIV, and 222 subjects received a single vaccination of TIV on Day 1. Of the 986 vaccinated elderly adults, 767 received a single vaccination of QIV, and 219 subjects received a single vaccination of TIV on Day 1.

Safety issues with the potential for major regulatory impact

According to the current EU Risk Management Plan (RMP); Version 3.0, Data lock point (DLP) of 29 February 2016, hypersensitivity is characterised as the only important identified risk for the seasonal influenza vaccine Influvac.

Postmarketing data

Not applicable as this is a new drug application. However, periodic safety update reports (PSUR) Numbers 17 (1 May 2011 to 30 April 2012) to Number 24 (1 September 2015 to 15 March 2016) inclusive for the TIV were submitted with this application. The QIV described in the sponsor's Summary of Clinical Safety is currently not marketed, therefore only post-marketing safety data from the marketed thiomersal-free TIV was presented and was summarised as part of the integrated safety analysis data. Based on market data, > 350 million doses of the current thiomersal free formulation of the subunit influenza vaccine have been administered between 2004 and 30 April 2016. Considering the large number of patients vaccinated with influenza vaccine and the low number of adverse events reported, the vaccine is regarded as safe and well tolerated.

Evaluator's conclusions on safety

In line with the scientific advice obtained from an European national authority, the exposure of around 1,500 adult subjects to QIV is deemed sufficient to demonstrate the safety of QIV. This exposure is lower than specified in the Note for Guidance on the 'Clinical Evaluation of New Vaccines' (EMA/CHMP/VWP/164653/2005), which recommends at least 3,000 subjects. However, QIV is not considered a completely new vaccine which would necessitate higher number of vaccinees in order to characterise safety. The extensive safety data collected with the related TIV, Influvac, is considered supportive for the QIV development, since the production process for QIV and Influvac are identical (aside from QIV containing both B strain lineages). Moreover, both B strain lineages have been alternatingly present in the TIV formulation over the years.

In Study INFQ3001, the safety profile of QIV in adults and elderly adults is generally similar to that observed for the comparator TIV vaccines within the study and similar to the integrated safety analyses derived from the 16 supporting immunogenicity studies. There was no concerning safety signal revealed with respect to solicited local and systemic reactogenicity, treatment related adverse events or serious adverse events in either the adult or elderly populations studied. The reviewer notes the slightly increased recorded incidence of arthralgia/joint pain post vaccination in the elderly population receiving the QIV vaccine, but despite this, the rates were still low. Overall, the clinical evaluator thinks that QIV has a clinically acceptable safety and tolerability profile in adults (≥ 18 years old) at least in the relatively small number of patients enrolled in this study exposed to single dose QIV. As Influvac has been marketed for several decades, no additional risks, which might be based on known class effects or known pharmacologic properties, are expected to occur.

First round benefit-risk assessment

First round assessment of benefits

The first round assessment of benefits is shown in Table 1, below.

Table 1: First round assessment of benefits

Indication	
Benefits	Strengths and Uncertainties
<ul style="list-style-type: none"> · Influvac Tetra in the proposed usage provides better coverage of the influenza B strains than the TIV; · QIV was immunogenic against all 4 strains it contains in both the adult and elderly populations; · the safety profile of this QIV is similar to trivalent inactivated influenza vaccines in general, and to the specific TIV comparators used in the pivotal efficacy study; · the inclusion of both B strains will overcome the problem of poor predictions of which B strain is likely to circulate, this has been problematic over the last few years and has led to misalignment of the B strain in the recommended TIV with the circulating B strain. 	<ul style="list-style-type: none"> · Paucity of data for the QIV in younger adults; · paucity of data for the QIV in adults and the elderly of Black or Asian ethnicity; · no data on immunogenicity or safety of repeat dosing with the QIV; · no data on immunogenicity or safety of repeat dosing with a QIV manufactured by a different company; · many other QIV flu vaccines available, so this QIV will not fill a 'gap in the market'.

First round assessment of risks

The risks of Influvac Tetra in the proposed usage are shown in Table 2, below.

Table 2: First round assessment of risks

Risks	Strengths and Uncertainties
<ul style="list-style-type: none"> • There is no data on the immunogenicity and safety profile in immunocompromised patients as such patients were specifically excluded from participation; • hardly any data for the QIV in subjects of Asian ethnicity; • nil data for the QIV in Australian indigenous ethnicity; this is relevant to the Australian population; • no data presented for the safety of QIV in lactating women, yet the product information states Influvac Tetra can be used during lactation. 	<ul style="list-style-type: none"> • (Related to first bullet point, left) Flagged in the PI; as detailed in the RMP, <i>'Other routine measures including monitoring and reporting of post-marketing safety data and signal detection in the immunocompromised'</i>. • (Related to bullet points 2 to 4, left), No indication from the TIV data that immunogenicity and safety of the QIV will be any different in these different ethnicities or in lactating women. Although there is no data on immunogenicity and safety of this QIV in pregnancy or lactation, use in pregnant and breast-feeding women is not an identified Safety Concern in the EU-RMP. There is a clear plan for the collection of safety data in pregnancy and lactation, which will be reported as a summary data in the PSURs.

First round assessment of benefit-risk balance

The first round assessment of benefit-risk balance is favourable.

First round recommendation regarding authorisation

The clinical evaluator recommends authorisation.

Clinical Questions

The clinical evaluator had no questions for the sponsor.

Second round benefit-risk assessment

Following the satisfactory assessment of the Influvac Tetra in the first round, the submission proceeded to Delegate's overview.

VI. Pharmacovigilance findings**Risk management plan**

The sponsor has submitted EU RMP version 3.0 dated 6 July 2016 (DLP 29 February 2016) and an Australian Specific Annex (ASA) in support of this application. The EU RMP covers several products including the TIVs for adults and children, and the QIV. As required by the RMP evaluator, the sponsor submitted an updated ASA version 2, dated 26 June 2017 with its post-first round evaluation response.

The proposed summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised below.

Table 3: Sponsor's summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Hypersensitivity to the active substances or to any of the excipients	Ü	–	Ü	–
Important potential risks	Non-febrile convulsions	Ü	–	Ü	–
	Adverse events following immunisation of possible autoimmune nature (for example Guillain-Barré syndrome, neuritis, encephalomyelitis, demyelinating disease, vasculitis, thrombocytopenia)	Ü	–	Ü	–
	Vaccination failure	Ü	–	Ü	–
Missing information	Use in pregnant and breast-feeding women ^{1,2}	Ü	–	Ü	–
	Use in children ^{1,2}	Ü	–	Ü	–
	Safety in immunocompromised patients	Ü	–	Ü	–

1) Australia-specific safety concerns; 2) Safety concerns reclassified as required by the first round evaluation report

Routine pharmacovigilance including enhanced surveillance in the EU is proposed to monitor all the safety concerns.

Routine risk minimisation is proposed to mitigate all the safety concerns.

Summary of recommendations at the second round RMP evaluation

Recommendation 1

This is an outstanding recommendation from the first round RMP evaluation report for the TGA Delegate. The Australian Immunisation Handbook includes the following recommendation:

‘The intramuscular route is preferred to the subcutaneous route because it causes fewer local adverse events.’

The sponsor has provided justification to its current approach of recommending deep subcutaneous (SC) injection as an alternative route of administration:

‘The sponsor acknowledges that the Australian Immunisation Handbook recommends intramuscular injection as the preferred route of administration for influenza vaccines. However, influenza vaccines may also be administered subcutaneously. This recommendation is based on studies which have demonstrated

that, for most vaccines, local adverse events are minimised and immunogenicity is enhanced by ensuring that the vaccine is deposited into the muscle and not the subcutaneous layer. Similar conclusions cannot be definitively drawn from the sponsor's clinical data for both the trivalent and quadrivalent influenza vaccine and post-marketing data of the trivalent influenza vaccine. In addition, this recommendation does not apply to all individuals. For example, the subcutaneous route is proposed as an alternative for individuals with underlying bleeding disorders as intramuscular injection may lead to haematomas.

Therefore, the sponsor proposes that the current administration instructions should remain, i.e. 'Influvac Tetra should be administered by intramuscular or deep subcutaneous injection'. The PI Instructions and Handling section also contains the text 'Please refer to the relevant National Immunisation Guidelines for full details on preparations and vaccine administration.' referring vaccinators to the Immunisation Guidelines.'

The RMP evaluator's recommendation remains for the TGA Delegate's consideration.

Recommendation 2

This is an outstanding recommendation from the first round RMP evaluation report. The sponsor has argued that safety surveillance conducted in New Zealand is sufficient to provide a signal for potential reactogenicity during the same influenza season in Australia. The sponsor should provide sufficient detail about the safety surveillance conducted in New Zealand for the TGA to assess this proposal, with particular regard to how the surveillance approach minimises under-reporting and provides timely information about potential changes in reactogenicity compared to the previous season's product.

The evaluator has noted that AusVaxSafety, the government funded national active vaccine safety surveillance initiative currently monitors influenza vaccine during influenza season between April and October. This local system using a sentinel surveillance network is sufficient to perform all the pharmacovigilance functions of the enhanced safety surveillance as described in the EU-RMP. If Influvac Tetra is included in AusVaxSafety or if the strains are identical to the preceding northern hemisphere season then there is no need for the sponsor to conduct a separate enhanced surveillance study in Australia. However, to accommodate the possibility that the vaccine is not included in AusVaxSafety, and the selected influenza strains for the Southern Hemisphere influenza season differ from those used in the preceding Northern Hemisphere influenza season, the sponsor should provide a brief description of an enhanced safety surveillance study for reactogenicity in Australia, and a commitment to develop and submit a full study protocol if requested. If so required, the protocol must be submitted with the relevant application for seasonal strain variation.

Recommendation 3

This is an outstanding recommendation from the first round RMP evaluation report for the TGA Delegate. There are discrepancies between the draft PI and the Australian Immunisation Handbook on persons with known egg allergy. The Australian Immunisation Handbook provides the following recommendation on persons with known egg allergy:

'Persons with a history of egg allergy (non-anaphylaxis) can receive an age-appropriate full dose of vaccine in any immunisation setting. This includes children that are sensitised (that is, skin prick or RAST test positive) but have not yet eaten egg. Persons with a history of anaphylaxis to egg should be vaccinated in medical facilities with staff experienced in recognising and treating anaphylaxis. The vaccinated person should remain under supervision in the clinic for at least 30 minutes after vaccination. A full age-appropriate vaccine dose should be used. There

is no need to split the dose into multiple injections (for example, a test and then remainder of the dose)'.

This advice is consistent with the updated recommendation provided by the Centres for Disease Control and Prevention in the United States for the 2016 to 2017 influenza season.

The sponsor has provided justification to its current approach:

'The sponsor acknowledges that publications and national immunisation recommendations are available regarding immunisation of persons with a history of egg allergies with an inactivated (egg-based) influenza vaccine. However, in the company-sponsored clinical trials (of both the trivalent and quadrivalent influenza vaccine), history of allergy to egg, chicken proteins, or other vaccine components was defined as exclusion criterion. In addition, the sponsor's post-marketing data of the trivalent vaccine do not allow any firm conclusions to be drawn on the use of our influenza vaccine in such individuals. Therefore, the sponsor requests to maintain the proposed contraindications [...] and administration instructions. In addition, the sponsor proposes to add the following text: '(refer to the relevant National Immunisation Guidelines for full details on preparations and vaccine administration.)' following the statement 'Immunisation should be postponed in patients with febrile illness or acute infection'.

The complete contraindication for Influvac Tetra is proposed below [...]:

'Hypersensitivity to the active substances, to any of the excipients and to residues of eggs (ovalbumin, chicken proteins), formaldehyde, cetrimonium bromide, polysorbate 80, or gentamicin.

Anaphylaxis following a previous dose of any influenza vaccine.

Immunisation should be postponed in patients with febrile illness or acute infection (refer to the relevant National Immunisation Guidelines for full details on preparations and vaccine administration).'

The RMP evaluator's recommendation remains for the TGA Delegate's consideration.

Wording for conditions of registration

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

No suggested wording for condition of registration could be provided as there are outstanding issues in the RMP.

VII. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

The quality summary recommends that there are no further objections to the registration of Influvac Tetra, inactivated QIV (surface antigen). However, the summary report does not include viral safety issues which are to be addressed separately by the sponsor with the viral safety unit.

Nonclinical

No nonclinical studies were conducted with the quadrivalent vaccine; previous studies with Influvac trivalent vaccine and some publications were submitted in response to a request by the reference member state for the EU application. The lack of new nonclinical studies with Influvac Tetra is consistent with EMA guidance for a new influenza vaccine based on an existing manufacturing process.

Although limited, the nonclinical data raise no objections to registration of Influvac Tetra vaccine. In relation to product information the sponsor has proposed a B1 pregnancy category whereas the nonclinical evaluation recommends a B2 category.^{9,10}

Clinical

The pivotal clinical Study INFQ3001 is not an 'efficacy' study, instead the immunogenicity data derived is used as a surrogate for clinical efficacy.

Immunological assay methods Anti-HA antibody response is an established correlate of protection against influenza in adults; therefore, HI titre was the primary outcome measure in the one submitted clinical study. Therefore, the primary objective was to demonstrate that the post-vaccination HI geometrical mean titres responses with QIV for each of the shared strains were non-inferior to those with the TIVs. The non-inferiority margin was set at a HI geometric mean titre (GMT) ratio of 1.5, which was in agreement with the scientific advice obtained from an EU national competent authority and was also in accordance with the margin recommended by FDA guidelines. As a secondary efficacy objective, the study aimed to demonstrate that the added B strain in QIV provided an antibody response superior to that with the TIV for the alternate B strain lineage. In addition, the immunogenicity of each of the strains in QIV and TIVs was further characterised by describing the derived serology parameters of seroconversion, and mean fold increase with respect to HI and VN antibody titres and by performing analyses in study population subsets according to age and pre-existing antibody status. Furthermore, cell mediated immunity values were described for a subset of subjects.

Details of the central laboratory performing the HI assays were provided by the sponsor.

In accordance with the guidelines indicated by EMA:

- Any HI result < 10 (= undetectable) was expressed as 5;
- Sera which have a titre ≥ 10 but < 40 are considered positive but not protective;
- Sera with a titre ≥ 40 are considered positive and protective.

Clinical efficacy (immunogenicity)

Study INFQ3001 is a Phase III, randomised, double blind, active controlled study in adults to assess the safety and immunogenicity of the sponsor's candidate QIV and its non-inferiority to the TIV.

⁹ Australian Pregnancy Category B2: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage.

¹⁰ Australian Pregnancy Category B1: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage.

The study was conducted at 20 sites in European countries between May 2015 and January 2016 and included men and women ≥ 18 years of age stratified 1:1 for age in adults (≥ 18 to ≤ 60 years) and elderly adults (≥ 61 years).

The study therapy was a single 0.5 mL dose of quadrivalent influenza subunit vaccine (with the strains recommended for the past influenza season NH2014/2015 administered by intramuscular injection. The HA content of the QIV batch as follows:

- A/California/7/2009 (H1N1)pdm09-like strain (A/California/7/2009, X-181) (16.9 μg HA/dose)
- A/Texas/50/2012 (H3N2)-like strain (A/Texas/50/2012, X-223A) (17.0 μg HA/dose)
- B/Massachusetts/2/2012-like strain (B/Massachusetts/2/2012, BX-51B) (15.3 μg HA/dose)
- B/Brisbane/60/2008 (wild type) (17.3 μg HA/dose).

The reference therapy was a single 0.5 mL dose of licensed Influvac (TIV) containing approximately 15 μg of HA antigen per virus strain, or a single 0.5 mL dose of TIV containing the alternate B strain.

Participants were randomly assigned to vaccination with QIV, TIV_(Vic) or TIV_(Yam), in a 7:1:1 ratio, respectively).

The primary efficacy objective was post-vaccination geometric mean haemagglutinin inhibition (HI) antibody titres against the shared strains compared with the trivalent influenza vaccines (TIV) with either the B strain of the Victoria (TIV_(Vic)) or the B strain of the Yamagata lineage (TIV_(Yam)). The primary efficacy endpoint was Day 22 geometric means of the HI titres against these strains between the QIV and TIVs. Non-inferiority will be inspected by calculating for each of the 2 A strains and each of the 2 B strains a 2-sided 95% CI for geometric mean ratios (GMRs) for the contrast TIV versus QIV. The non-inferiority margin has been set to 1.5 non-inferiority of QIV to TIV will be concluded if for all 4 strains the upper limit of the 95% CI falls below 1.5. The Per protocol data set was the primary analysis.

Secondary efficacy objectives were:

1. To demonstrate in subjects ≥ 18 of age the superiority of QIV to TIV_(Vic) and TIV_(Yam) with respect to post-vaccination geometric mean HI antibody titres against the alternate lineage B strain;
2. To describe the immunogenicity for HI and VN antibody titres using the derived serology parameters seroconversion and geometric mean fold increase for each of the strains in QIV and TIV, in adults (≥ 18 to ≤ 60 years of age) and elderly (≥ 61 years of age);
3. To describe the immunogenicity for HI and VN antibody titres in study population subsets according to age and pre-existing antibody status for each of the strains in QIV and TIV.
4. To describe cell mediated immunity values for a subset of subjects.

The number of subjects to be allocated to treatment totals 1,980: 1, 5380 QIV: 221 TIV_(Vic):221 TIV_(Yam). The number of subjects vaccinated was 1535 QIV; 221 TIV_(Vic) and 221 TIV_(Yam). Attachment 2 gives the numbers in the Safety population, the Full analysis set (FAS) population and the Per Protocol (PP) population.

Attachment 2 outlines the baseline demographic data. The majority of subjects were White (99.5%); 43.4% were male and 56.6% female. The mean (SD) age at screening was 55.7 (17.7) years. Adults had a mean age of 39 (SD = 12.6) years and a median age of 39 years (range: 18 to 60 years). Elderly adults had a mean age of 69 (SD = 6.3) years and

a median age of 68 years (range: 60 to 92 years). The majority of subjects across vaccination groups had not previously received a vaccine against seasonal influenza (51.2% in the QIV group, 54.3% in the TIV_(Vic) group, and 52.9% in the TIV_(Yam) group) and had not experienced an ILI since the start of the last season (99.2% in the QIV group, 99.5% in the TIV_(Vic) group, 99.1% in the TIV_(Yam) group).

For the primary efficacy outcome for all four strains the upper limit of the 95% CI for the HI geometric mean ratio (GMR; TIV versus QIV) fell below the pre-defined non-inferiority margin of 1.5, meaning that the non-inferiority of QIV to TIV was demonstrated. Results were similar for FAS analysis.

For the secondary outcome, superiority of QIV versus TIV against alternate lineage B strains, For both B strain lineages, the HI GMT of the TIV group was less than half of the GMT in the QIV group: 64.1 versus 153.1 (B-Victoria lineage) and 47.2 versus 101.9 (B-Yamagata lineage). Both differences were statistically significant ($P < 0.0001$, both comparisons). Thus, the HI antibody responses elicited by the B strain antigens were superior to the antibody responses elicited by cross-reactivity antigens of the alternate B strain lineages. The secondary efficacy analysis was similar for the PP set.

In all vaccination groups, the HI antibody responses declined with increasing age for all four strains. In both adult subjects and elderly subjects, GMTs increased in all vaccination groups for the FAS from Day 1 (pre-vaccination) to the Day 22 visit after vaccination for all 4 strains. Both B strain lineages induced limited cross-reactivity.

Geometric Mean Fold increases in HI titres, seroconversion rates and post-vaccination increases in HI titres are shown for adults (FAS) and for elderly FAS are shown in Attachment 2.

For the A (H3N2) strain in adult subjects, the post-vaccination HI titres ≥ 40 were reported in 97.8% in the QIV group compared to 95.9% in the pooled TIV group. In elderly subjects for A (H3N2) strain, the post-vaccination HI titres ≥ 40 were reported in 95.7% in the QIV group compared to 96.3% in the pooled TIV group.

For the A (H1N1) strain in adult subjects, the post-vaccination HI titres ≥ 40 were reported in 94.6% in the QIV group compared to 93.6% in the TIV group. In elderly subjects, the post-vaccination HI titres ≥ 40 were reported in 85.3% in the QIV group compared to 88.9% in the pooled TIV group.

For the B strain Victoria lineage in adult subjects, post-vaccination HI titres ≥ 40 were reported in 92.8% in the QIV group compared to 89.1% in the TIV_(Vic) group and 79.1% in the TIV_(Yam) group. In elderly subjects, the post-vaccination HI titres ≥ 40 were reported in 80.8% in the QIV group compared to 81.5% in the TIV_(Vic) group and 63.0% in the TIV_(Yam) group.

For the B strain Yamagata lineage in adult subjects, post-vaccination HI titres ≥ 40 were reported in 91.6% in the QIV group compared to 78.2% in the TIV_(Vic) group and 90.0% in the TIV_(Yam) group. In elderly subjects, the post-vaccination HI titres ≥ 40 were reported in 73.3% in the QIV group compared to 51.8% in the TIV_(Vic) group and 73.6% in the TIV_(Yam) group.

In both adult subjects and elderly subjects, the GMTs for virus neutralisation increased in all vaccination groups from Day 1 (pre-vaccination) to the Day 22 visit (post-vaccination) for all 4 strains.

In an analysis performed across 16 supportive studies of Influvac TIV (see Attachment 2) the post-vaccination GMTs of the QIV and TIV formulations used in Study INFQ3001 are within the expected range of the pooled post-vaccination GMTs of the 16 TIV studies.

Immunogenicity conclusion

Study INFQ3001 demonstrates the immunogenicity of Influvac Tetra in adults aged 18 to 60 years and the elderly aged ≥ 61 years against all 4 strains of influenza virus contained within the vaccine. Standard methodology to demonstrate immunogenicity was utilised. Importantly, the added B strain provides superior immunogenicity without affecting the antibody response to the other strains and there is no safety cost. Seroprotection rates for all 4 strains in the QIV were higher in adults compared to the elderly, but nevertheless high in both groups. Lower seroprotection in the elderly is not a unique finding for this vaccine and not a concern in the clinical evaluation report.

Clinical safety

Methods for analysis of safety in clinical Study INFQ3001 are described in Attachment 2. Local reactions and systemic reactions were reported within 7 days after vaccination, adverse events were reported for 22 days post-vaccination and with 6 month safety follow-up for SAEs and new chronic illnesses.

1535 adults received a single dose of the QIV. Of the 990 vaccinated adult subjects aged 18 to 60 years, 768 received a single vaccination of QIV, and 221 subjects received a single vaccination of TIV on Day 1. Of the 986 vaccinated elderly adults, 767 received a single vaccination of QIV, and 221 subjects received a single vaccination of TIV on Day 1.

For adults aged 18 to 60 years, 4.5% of subjects reported ≥ 1 treatment emergent adverse event up to the Day 22 visit; 4.8% subjects in the QIV group and 3.6% subjects in the TIV group. A total of 0.5% and 0.9% of the subjects in the QIV and TIV groups, respectively, had ≥ 1 treatment emergent adverse event considered to have a reasonable possibility for a causal relationship with the study vaccine. 3 subjects (0.3%) in the QIV group reported treatment emergent adverse events that were severe. However, the proportion of subjects with treatment emergent adverse events was similar across vaccination groups. Treatment emergent adverse events were reported most frequently in the System Organ Class (SOC) of 'Infections and infestations' (14 adult subjects (1.8%) in the QIV group and 2 adult subjects (0.9%) in the TIV group). No treatment emergent adverse event was reported in > 2 adult subjects for any Preferred Term (PT) in either vaccination group.

For elderly adults, 3.5% of subjects reported ≥ 1 treatment emergent adverse event up to the Day 22 visit; 3.8% subjects in the QIV group and 2.7% subjects in the TIV group. A total of 0.8% and 0.9% of subjects in the QIV and TIV groups, respectively, had ≥ 1 treatment emergent adverse event that was considered to have a reasonable possibility for a causal relationship with the study vaccine. Overall, 4 subjects (0.4%) reported 4 treatment emergent adverse events that were severe in severity. However, the proportion of subjects with treatment emergent adverse events was similar across vaccination groups. Treatment emergent adverse events were reported most commonly in the 'Infections and infestations' SOC (11 subjects (1.4%) in the QIV group and 2 elderly adults (0.9%) in the TIV group). No treatment emergent adverse event was reported in > 2 elderly adults in either vaccination group. No flagging occurred in this age group.

Local reactions in Study INFQ3001 in adults within 7 days after vaccination were generally reported at a low rate ($< 10\%$), except for vaccination site pain (24.9% in the QIV group and 18.5% in the TIV group). Local reactions in Study INFQ3001 in elderly adults within 7 days after vaccination were generally reported at a low rate ($< 5\%$), except for injection site pain (7.6% in the QIV group and 5.9% in the TIV group). Most local reactions were mild or moderate in severity.

Systemic reactions in Study INFQ3001 reported within 7 days after vaccination were most frequently headache and fatigue/tiredness in both adults and the elderly in both vaccination groups. Most systemic reactions were mild or moderate in both the adults and elderly. In adults, severe reactions were reported in $\leq 0.3\%$ in the QIV group and $\leq 0.9\%$ in

the TIV group in adults. In the elderly, severe reactions were reported in $\leq 0.7\%$ in the QIV group and $\leq 0.5\%$ in the TIV group. One reaction (arthralgia/joint pain, 5.8% (QIV) versus 2.3% (TIV)) in the elderly reached statistical significance thus was flagged as having a potentially higher reporting rate for elderly subjects in the QIV group.

No deaths associated with treatment emergent serious adverse events (TESAE) were reported to Day 22 in Study INFQ3001. Death post Day 22 to Month 6 post-vaccination was reported for 1 adult subject with the treatment emergent serious adverse event of severe cardiac disorder which was considered unrelated to study vaccine. Death post Day 22 to Month 6 was reported for 4 elderly subjects with treatment emergent serious adverse event: oesophageal cancer, pancreatic cancer, hepatic failure, cardiac failure. None of the treatment emergent serious adverse events were considered to have a reasonable possibility for a causal relationship with the study vaccine.

No pregnancies were reported to the Day 22 visit. 5 pregnancies were reported post Day 22 to Month 6 post-vaccination. 2 subjects had spontaneous abortions and one subject had an elective termination. These events were judged as unrelated to study vaccination. 2 subjects had full term pregnancies with normal outcomes.

Treatment emergent serious adverse events up to the Day 22 visit were reported in 2 subjects in adults (cartilage injury, hand fracture). Treatment emergent serious adverse events up to the Day 22 visit were reported in 5 (0.5%) elderly subjects. In the QIV group 1 subject each reported abdominal wall abscess, atrial fibrillation, foot fracture, and rotator cuff syndrome. Sub-acute endocarditis and arterial embolism were reported in 1 subject from the TIV group.

Treatment emergent serious adverse events from Day 22 to Month 6 post-vaccination in adults were similar across the vaccination groups (1.3% and 1.8% in the QIV and TIV groups, respectively)

Treatment emergent serious adverse events from Day 22 to Month 6 post-vaccination in the elderly were similar across the vaccination groups (3.9% and 4.1% in the QIV and TIV groups, respectively). No treatment emergent serious adverse reported in > 1 subject for any PT in either vaccination group, except cerebrovascular accident reported in 2 subjects (0.3%) in the QIV group.

None of the treatment emergent serious adverse were considered related to the study vaccine by the investigator.

New chronic illness (NCI) from Day 22 to Month 6 post-vaccination in adults was similar across the groups (1.3% and 1.4% in the QIV and TIV groups, respectively). No new chronic illness reported in > 1 subject for any PT in either vaccination group, except spinal osteoarthritis reported in 2 subjects (0.3%) in the QIV group. None of the NCIs were considered to have a reasonable possibility for a causal relationship with the study vaccine by the Investigator.

New chronic illness from Day 22 to Month 6 post-vaccination in the elderly was similar across the groups (4.0% and 2.3% in the QIV and TIV groups, respectively). No New chronic illness was reported in > 1 subject for any PT in either vaccination group, except for the following illnesses in the QIV group: cataract reported in 5 subjects (0.7%); osteoarthritis reported in 3 subjects (0.4%); and gastroenteritis, atrial fibrillation, and hypothyroidism each reported in 2 subjects (0.3%). None of the new chronic illnesses were considered related to the study vaccine by the investigator.

Overall, 11 subjects (0.6%) prematurely withdrew from Study INFQ3001. The number of premature withdrawals was 8 subjects (0.5%) assigned to QIV, 1 subject (0.5%) to TIV_(Vic) and 2 subjects (0.9%) to TIV_(Yam). Reasons reported: withdrawal of consent (4 subjects), adverse events (3 subjects with fatal treatment emergent adverse events, lost to follow up

(3 subjects) and administrative (1 subject). No subject reported a treatment emergent adverse event up to the Day 22 visit leading to study termination.

Conclusions on clinical safety

In line with the scientific advice obtained from a national authority, the exposure of around 1,500 adult subjects to QIV is deemed sufficient to demonstrate the safety of QIV.

QIV is not considered a completely new vaccine which would necessitate higher number of subjects in order to characterise safety. In Study INFQ3001, the safety profile of QIV in adults and elderly adults is generally similar to that observed for the comparator TIV vaccines within the study and similar to the integrated safety analyses derived from the 16 supporting immunogenicity studies. The reviewer notes the slightly increased recorded incidence of arthralgia/joint pain post-vaccination in the elderly population receiving the QIV vaccine, but despite this, the rates were still low, 5.8% QIV versus 2.3% TIV.

First round benefit-risk assessment

Benefits are listed as:

1. Influvac Tetra in the proposed usage provides better coverage of the influenza B strains than the TIV;
2. QIV was immunogenic against all 4 strains it contains in both the adult and elderly populations;
3. the safety profile of this QIV is similar to trivalent inactivated influenza vaccines in general and to the specific TIV comparators used in the pivotal efficacy study.

The clinical evaluation identifies as uncertainties in respect of benefits: paucity of data in younger adults, paucity of data adults of black or Asian ethnicity, no data on repeat dosing with QIV, no data on repeat dosing with a QIV manufactured by a different company. There are no data in this submission on administration of QIV other than by the IM route.

The clinical evaluation report lists as risks:

1. There is no data on the immunogenicity and safety profile in immunocompromised patients as such patients were specifically excluded from participation;
2. hardly any data for the QIV in subjects of Asian ethnicity;
3. nil data for the QIV in Australian indigenous ethnicity, this is relevant to the Australian population; and
4. no data presented for the safety of QIV in lactating women, yet the product information states Influvac Tetra can be used during lactation.

The clinical evaluation report notes that TIV data do not suggest immunogenicity and safety will differ with different ethnicities or in pregnant or lactating women. There is a clear plan for the collection of safety data in pregnancy and lactation, which will be reported as a summary data in the PSURs.

The clinical evaluation report recommends authorisation of Influvac Tetra, inactivated quadrivalent influenza vaccine (surface antigen).

RMP evaluation

The second round RMP evaluation identifies 3 outstanding recommendations (to which the sponsor has responded).

Recommendation 1

'The Australian Immunisation Handbook includes a recommendation that *'the intramuscular route is preferred to the SC route because it causes fewer local adverse events'*. The sponsor has provided justification to its current approach of recommending deep subcutaneous injection as an alternative route of administration.

Sponsor's response: The sponsor acknowledges that the Australian Immunisation Handbook recommends intramuscular injection as the preferred route of administration for influenza vaccines. However, influenza vaccines may also be administered subcutaneously. This recommendation is based on studies which have demonstrated that, for most vaccines, local adverse events are minimised and immunogenicity is enhanced by ensuring that the vaccine is deposited into the muscle and not the subcutaneous layer. Similar conclusions cannot be definitively drawn from the sponsor's clinical data for both the trivalent and quadrivalent influenza vaccine and post-marketing data of the trivalent influenza vaccine. In addition, this recommendation does not apply to all individuals. For example, the subcutaneous route is proposed as an alternative for individuals with underlying bleeding disorders as intramuscular injection may lead to haematomas.

The most recent sponsor proposal for PI is: *'Influvac Tetra should be administered by intramuscular or deep subcutaneous injection, whereas the intramuscular route is preferred'*.

The 'Handling section' also contains the text: *'Please refer to the relevant National Immunisation Guidelines for full details on preparations and vaccine administration'*.

The Delegate considers this text is acceptable.

Recommendation 2

The sponsor has provided justification to why an enhanced safety surveillance study for reactogenicity in Australia is not required. The sponsor has argued that *'presently, although Influvac Tetra is not included in the National Immunization Program in Australia, it is the sole influenza vaccine included in the National Immunization Program in New Zealand with approximately one million doses distributed each year. The existing routine pharmacovigilance monitoring requirement and associated large scale use in New Zealand, together with coordinated global oversight of safety information through the company's global safety function would support the same objectives as those set out in the program. Therefore, the sponsor proposes that an Enhanced Passive Safety Surveillance Program (or proposal to conduct this program) is not required currently given the above proposed condition(s) have been met for the same influenza season in Australia.'*

The second round RMP evaluation requests the sponsor to provide sufficient detail about the safety surveillance conducted in New Zealand for the TGA to assess this proposal, with particular regard to how the surveillance approach minimises under-reporting and provides timely information about potential changes in reactogenicity compared to the previous season's product. The evaluation also comments that *'to accommodate the possibility that the vaccine is not included AusVaxSafety, and the selected influenza strains for the Southern Hemisphere influenza season differ from those used in the preceding Northern Hemisphere influenza season, the sponsor should provide a brief description of an enhanced safety surveillance study for reactogenicity in Australia, and a commitment to develop and submit a full study protocol if requested'*. The sponsor has responded with a brief description of an enhanced safety surveillance study for reactogenicity which is included in the revised RMP ASA version 3.0.

Recommendation 3

There are discrepancies between the draft PI and the Australian Immunisation Handbook on persons with known egg allergy.

The sponsor has provided justification to its current approach: 'The sponsor acknowledges that publications and national immunisation recommendations are available regarding immunisation of persons with a history of egg allergies with an inactivated (egg based) influenza vaccine. However, in the company-sponsored clinical trials (of both the TIV and QIV), history of allergy to egg, chicken proteins, or other vaccine components was defined as exclusion criterion. In addition, the sponsor's post-marketing data of the trivalent vaccine do not allow any firm conclusions to be drawn on the use of our influenza vaccine in such individuals. Therefore, the sponsor requests to maintain the proposed contraindications (as proposed in its response) and administration instructions. In addition, the sponsor proposes to add the following text: '(refer to the relevant National Immunisation Guidelines for full details on preparations and vaccine administration.)' following the statement 'Immunisation should be postponed in patients with febrile illness or acute infection'.

The Delegate considers the proposed statements under 'Contraindications' can be accepted.

Risk-benefit analysis

Delegate's considerations

Discussion

The submission is supported by one clinical study conducted in Europe in a single season involving approximately 1500 adult and elderly subjects. There was a slightly increased recorded incidence of arthralgia/joint pain post vaccination in the elderly population who received the QIV vaccine, but despite this, the rates were still low, 5.8% (QIV) versus 2.3% (TIV). The Delegate concurs with the clinical evaluator's conclusion that these data are sufficient to support registration of Influvac QIV given the extensive support and clinical experience with Influvac TIV.

As a result of the TGA's second round viral safety assessment, further viral safety test data to demonstrate conformance with Ph. Eur. General Monograph 01/2013:0153 Vaccines for human use, is requested to be provided as a post registration commitment, and this was accepted by the sponsor.

The Delegate also notes that there is a specific Ph. Eur. Monograph 0869 (egg-derived influenza vaccines (inactivated, subunit antigen)) vaccines which includes testing for freedom from extraneous agents. The sponsor has responded that they commit to conducting testing as required by Ph Eur 2.6.16.

The nonclinical evaluation recommends a B2 Use in pregnancy category although a B1 pregnancy category was initially proposed. The WHO Expert Committee on Biological Standardization has recently established a guideline on inactivated influenza vaccines for use in pregnant women. The TGA and Australian Health Department are participating in an evidence review on safety of inactivated influenza vaccines in pregnancy that may facilitate appropriate labelling regarding use of IIVs in pregnant women. In the interim the Delegate would support the initially proposed use in Pregnancy Category B1.¹⁰

The clinical evaluation report notes vaccines were administered IM in the deltoid muscle of the upper arm in Study INFQ3001. The proposed PI also includes administration by deep subcutaneous injection. The second round RMP evaluation in Recommendation 1 risk management plan has included a sponsor response on The Australian Immunisation Handbook recommendation that '*The intramuscular route is preferred to the subcutaneous route because it causes fewer local adverse events.*' It is also relevant that the product could be supplied in 3 presentations: (1) syringe with 16 mm needle, (2) syringe with 25 mm needle and (3) syringe without needle. In this regard, the sponsor has confirmed that for

the southern hemisphere 2018 season, the sponsor plans to supply Influxac Tetra with the 16 mm needle presentation only. This may not be a length that allows reliable intramuscular administration in all adult patient groups. The Delegate accepts that the sponsor response that the subcutaneous route is proposed as an alternative for individuals with underlying bleeding disorders as intramuscular injection may lead to haematomas. The Delegate accepts the sponsor's most recent proposed wording '*Influxac Tetra should be administered by intramuscular or deep subcutaneous injection, whereas the intramuscular route is preferred*' and with a cross reference '*Please refer to the relevant National Immunisation Guidelines for full details on preparations and vaccine administration*'.

The TGA has not yet adopted the Guideline on Influenza Vaccines Non-clinical and Clinical Module EMA/CHMP/VWP/457259/2014 (adopted in Europe 1 February 2017) but is considering adoption with annotation. The RMP Recommendation 2 reflects post-authorisation pharmacovigilance requirements for seasonal influenza vaccines and the need conduct of enhanced safety surveillance will be determined on a case to case basis. The second round RMP evaluation requests the sponsor to provide sufficient detail about the safety surveillance conducted in New Zealand for the TGA to assess this proposal for conduct of enhanced safety surveillance. The sponsor has responded '*As proposed by the TGA, and to accommodate for the possibility that the vaccine is not included in AusVaxSafety, and, the selected influenza strains for the southern hemisphere season differ from those used in the preceding northern hemisphere influenza season, a brief description of an enhanced safety surveillance study for reactogenicity is included in the revised RMP ASA version 3.0. Upon request by the TGA, Mylan will submit a full protocol for this study and this information will be provided with the relevant application for seasonal strain variation*'.

RMP recommendation 3 (see above) notes discrepancies between the draft PI and the Australian Immunisation Handbook on persons with known egg allergy. The sponsor has provided justification to its current approach.

The sponsor proposed approach is considered acceptable by the Delegate.

Summary of issues

The submission is supported by one clinical study conducted in Europe in a single season involving approximately 1500 adult and elderly subjects. There was a slightly increased recorded incidence of arthralgia/joint pain post vaccination in the elderly population receiving the QIV vaccine, but despite this, the rates were still low, 5.8% QIV versus 2.3% TIV. The Delegate concurs with the clinical evaluator's conclusion that these data are sufficient to support registration of Influxac QIV given the extensive support and clinical experience with Influxac TIV.

The outcome of the TGA's viral safety assessment requires further viral safety testing by the sponsor.

The nonclinical evaluation requested use in pregnancy categorisation to be amended from proposed Category B1 to B2.^{9,10} The TGA and Australian Health Department are participating in an evidence review on safety of influenza vaccines in pregnancy, specifically whether Category A is more appropriate pregnancy category for inactivated influenza vaccines.¹¹

The RMP has raised the alternative subcutaneous route of administration as an issue. The clinical Study INFQ3001 used only the intramuscular route of administration. The proposed PI now states the intramuscular route of administration is preferred. For the SH 2018 season, the sponsor plans to supply Influxac Tetra with the 16 mm needle

¹¹ Australian Pregnancy Category A: Drugs which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed.

presentation only which may not allow reliable intramuscular administration in all patient groups.

The second round RMP evaluation requests the sponsor to provide sufficient detail about the safety surveillance conducted in New Zealand for the TGA to assess this proposal for conduct of enhanced safety surveillance. The sponsor has responded:

'As proposed by the TGA, and to accommodate for the possibility that the vaccine is not included in AusVaxSafety, and, the selected influenza strains for the SH season differ from those used in in the preceding Northern Hemisphere influenza season , a brief description of an enhanced safety surveillance study for reactogenicity is included in the revised RMP ASA version 3.0. Upon request by the TGA, the sponsor will submit a full protocol for this study and this information will be provided with the relevant application for seasonal strain variation'.

There are discrepancies between the draft PI and the Australian Immunisation Handbook on contraindications in persons with known egg allergy.

Proposed action

The Delegate had no reason to say, at the time, that the application for Influvac Tetra inactivated quadrivalent influenza vaccine (surface antigen), should not be approved for registration, subject to Advisory Committee on Vaccines (ACV) advice.

Request for ACV advice

The committee is requested to provide advice on the following specific issue:

1. Is the clinical data package sufficient to support registration of Influvac Tetra?

The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from sponsor

Introduction

The sponsor submitted an application in July 2016 for approval to register Influvac Tetra as an inactivated QIV (surface antigen) for the following proposed indication:

'For the prevention of influenza caused by influenza virus, types A and B.

For full details regarding recommendations for influenza vaccination, please refer to the relevant National Immunisation Guidelines.

Influvac Tetra is indicated in adults (18 years of age and older)'.

The submission was supported by one pivotal Phase III clinical study (Study INFQ3001) in approximately 1500 adults and elderly subjects supporting the proposed indication. Reliance was placed on the extensive clinical trial database and post-approval pharmacovigilance data of the TIV Influvac.

Delegate's proposed action

Subject to ACV advice, there is no reason to object to registration.

Quality

The sponsor acknowledges that there are no further objections to the registration of Influvac Tetra from the quality perspective.

Viral safety

The sponsor has committed to conduct testing as required by the Ph. Eur. 2.6.16 and will submit the testing plan and protocol.

Nonclinical

The sponsor acknowledges that no objections to the registration of Influvac Tetra were raised from nonclinical data and welcomes the safety evidence review initiative, as noted by the Delegate, undertaken by the TGA and Australian Health Department to determine whether a Pregnancy Category A is appropriate for all influenza vaccines in Australia.¹¹

Clinical

The submission was supported by one pivotal Phase III clinical study (Study INFQ3001) in approximately 1500 adults and elderly subjects supporting the proposed indication, and relies on the extensive trial database and post-approval pharmacovigilance data of the TIV Influvac.

In Study INFQ3001, the primary and secondary immunogenicity objectives were fully met:

- The immune response as defined by post-vaccination HI titres of the 4 strains contained in Influvac Tetra was non-inferior to the same strains in the marketed Influvac and in Influvac with the alternative B-strain; thus there is no sign of immune-interference with existing strains.
- For the post-vaccination HI titres in each of the B strains not contained in the TIV, Influvac Tetra was superior.
- The derived HI serological parameters seroprotection, seroconversion and mean fold increase for each of the strains in Influvac Tetra met the criteria that as defined by the CHMP, both for adult and elderly subjects.¹² VN data were in line with the HI data. The safety objective was also fully met:
 - The presence of a second B-strain in Influvac Tetra did not influence the reactogenicity and overall safety profiles comparable with those of the trivalent vaccines.

Based on the clinical evidence supporting Influvac Tetra, the extensive clinical data and post-marketing experience in over 80 countries gained over more than 30 years, and including in Australia since first supplied more than 12 years ago, with TIV Influvac the sponsor considers that the application is adequately supported.

The sponsor concurs with the Delegate and the clinical evaluation report conclusion stating that the clinical data submitted are sufficient to support the registration of quadrivalent Influvac Tetra given the extensive support and clinical experience with TIV Influvac.

RMP

The sponsor acknowledges the EMA Guideline CHMP/VWP/457259/2014, referenced by the Delegate, has not yet been adopted by the TGA though it is under consideration for adoption with annotation. If the EMA guideline is adopted, the sponsor will also adopt requirements as annotated by TGA.

Summary

The sponsor looks forward to the opportunity to negotiate a mutually agreeable Product Information document in support of registration of Influvac Tetra (inactivated QIV, surface antigen).

¹² CHMP = Committee for Medicinal Products for Human Use; European Medicines Agency (EMA).

Conclusion

Based on the quality, efficacy and safety evidence supporting Influvac Tetra and the extensive clinical data and postmarketing experience gained with TIV Influvac the sponsor considers that the application for Influvac Tetra to be adequately supported for use in adults 18 years of age and older for the above proposed indication.

Advisory committee considerations

The Advisory Committee on Vaccines (ACV) resolved to recommend to the TGA Delegate of the Secretary that taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Influvac Tetra inactivated QIV (surface antigen) to have an overall positive benefit-risk profile for the indication:

'For the prevention of influenza caused by influenza virus, types A and B. For full details regarding recommendations for influenza vaccination, please refer to the relevant National Immunisation Guidelines. Influvac Tetra is indicated in adults (18 years of age and older).'

In making this recommendation the ACV:

- was of the view that the immunogenicity data were adequate, although there were no data comparing Influvac Tetra to another QIV;
- was of the view that the safety data were adequate;
- noted the limited data or absence of data in various population groups;
- noted that there were no data to support the option for administration of the vaccine as a deep subcutaneous injection;
- supported the use of 25 mm needles as more clinically appropriate for the adult Australian population than 16 mm needles;
- supported the approach of the Australian Immunisation Handbook and Australasian Society of Clinical Immunology and Allergy (ASCIA) on vaccination of egg-allergic individuals.

The ACV advised the following in response to the Delegate's specific questions on the submission:

1. *Is the clinical data package sufficient to support registration of Influvac Tetra?*

The ACV was of the view that the clinical data were limited but sufficient to support registration of the vaccine.

The ACV noted that the vaccine is to be provided as a prefilled syringe for injection with an attached 16 mm needle. The committee discussed:

- Syringe length and route of administration:
 - body mass of the Australian adult population;
 - likely increase in local adverse effects with deep SC compared to IM; use of longer needles has been associated with less redness or swelling than occurs with shorter needles; and
 - the lack of information on the needle length(s) used in the pivotal trial.

The committee agreed that the 16 mm needle may not allow reliable IM administration in all patient groups and may result in unintended deep subcutaneous injection. The ACV was concerned that no evidence was provided to support that IM and deep SC administration would provide similar immunogenicity.

The committee noted the US Advisory Committee on Immunization Practices (ACIP) recommendation to use a 25 mm needle for IM injection in the deltoid muscle of the arm of adults; for men over 118 kg body weight and women over 90 kg bodyweight, a 38 mm needle is recommended. Some experts recommend a 16 mm needle for men and women who weigh less than 60 kg. The committee concluded that the option for administration as a deep subcutaneous injection was inconsistent with the clinical trial data, and that inclusion of a 16 mm needle in the vaccine to be supplied in Australia was generally not clinically appropriate for the adult Australian population to be vaccinated. The ACV noted the advice in the current edition of the Australian Immunisation Handbook, including that the majority of persons with egg allergy, including anaphylaxis, can be safely vaccinated with influenza vaccines that contain less than 1 microgram (1000 nanograms) ovalbumin per dose.

- Egg allergy:

The ACV also noted guidelines recently published by the ASCIA, which additionally advises that egg-allergic individuals do not have an increased risk of allergic reactions to influenza vaccines. The ASCIA guideline states '*A recent review of 28 studies comprising 4,315 subjects with egg allergy (including 656 subjects with a history of egg anaphylaxis) showed no severe reactions after influenza vaccination*'.

Sponsor's post ACV response

Sponsor responded to the Delegate's request for a response to the ACV support for use of 25 mm needles for the adult population and ACV support for AIH and ASCIA statements on vaccination of egg-allergic individuals, as follows.

- Syringe length and route of administration

'Influvac Tetra equipped with the 16 mm needle is the presentation currently supplied to the worldwide market, including New Zealand, where Influvac Tetra is the sole influenza vaccine supplied on the National Immunisation Program for 2018. The sponsor intends for Influvac Tetra to be registered for administration by either intramuscular (IM) or subcutaneous (SC) injection.

The current Australian Immunisation Handbook (Table 2.2.1) shows that the route of administration for influenza vaccines used in Australia is by IM or SC injection with a preference for IM. The sponsor acknowledges and agrees with the TGA's view that the 25 mm needle is the preferred needle length.

The current Influvac Tetra submission includes the following proposed needle options: 16 mm, 25 mm, and without needle. The sponsor is currently working towards making Influvac Tetra equipped with a 25 mm needle available to the Australian and New Zealand markets in the future"

- Egg allergy

The sponsor proposed Contraindication wording. The sponsor also considered that the proposed addition of the statement '*Refer to the relevant National Immunisation Guidelines for full details on preparations and vaccine administration*' will allow healthcare professionals to be made aware of the available options in order to make an informed clinical decision on administration of the vaccine in this patient group.

Outcome

Based on a review of quality, safety and efficacy, the TGA approved the registration of:

- Influvac Tetra influenza virus haemagglutinin 0.5 mL vaccine prefilled syringe without needle
- Influvac Tetra influenza virus haemagglutinin 0.5 mL vaccine prefilled syringe with 16 mm needle
- Influvac Tetra influenza virus haemagglutinin 0.5 mL vaccine prefilled syringe with 25 mm needle

The approved indication for these therapeutic goods is:

'For the prevention of influenza caused by influenza virus, types A and B. For full details regarding recommendations for influenza vaccination, please refer to the relevant National Immunisation Guidelines

Influvac Tetra is indicated in adults (18 years of age and older).'

Specific conditions of registration applying to these goods

1. The sponsor must provide evidence to satisfy the TGA within 3 months of the date of ARTG registration that Influvac Tetra:
 - Conforms to the tests which are invoked by the European Pharmacopoeia (Ph. Eur.) General Monograph 01/2013:0153 Vaccines for human use that control for non-specific extraneous agents including non-enveloped, non-haemagglutinating viruses. These tests are specified in Ph. Eur. Methods of Analysis 2.6.16 Tests for extraneous agents in viral vaccines for human use; or
 - has alternative measures applied that are effective at managing the risk of contamination with unknown non-enveloped, non-haemagglutinating viruses, to an equivalent or greater level than the measures prescribed by Ph. Eur. 2.6.16.

Any extension beyond this time frame would be subject to written agreement by the TGA.
2. The Influvac EU-RMP, version 3.0, dated 6 July 2016, with ASA version 3.0 dated 22 August 2017, included with Submission PM-2016-02725-1-2, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.
3. It is a condition of registration that all independent batches of Influvac Tetra, inactivated quadrivalent influenza vaccine (surface antigen) imported into Australia are not released for sale until samples and the manufacturer's release data have been assessed and you have received notification acknowledging release from the Laboratories Branch, TGA.

Therapeutic Goods Administration

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