OPTAFLU® 2008

NAME OF MEDICINE

Optaflu® 2008

Inactivated influenza virus vaccine (surface antigens), prepared in cell cultures.

DESCRIPTION

Influenza virus surface antigens (haemagglutinin and neuraminidase)*, inactivated, of the following strains:

A/Solomon Islands/3/2006 (H1N1)-like, 15µg micrograms HA** A/Wisconsin/67/2005 (H3N2)-like15µg micrograms HA** B/Malaysia/ 2506/2004-like15µg micrograms HA**

* propagated in Madin Darby Canine Kidney (MDCK) cells

** haemagglutinin

The type and amount of viral antigens in Optaflu conform to the requirements of the World Health Organisation (WHO) for the Northern Hemisphere winter of 2007-2008. The strains chosen for vaccine manufacture are endorsed by the WHO as being antigenically equivalent to the reference virus.

Each 0.5 mL vaccine dose contains 15µg haemagglutinin of each of the recommended strains. The vaccine preparation also contains Sodium chloride, Potassium chloride, Potassium dihydrogen phosphate, Sodium phosphate-dibasic, Magnesium chloride and Water for Injections. The vaccine may contain residues of the following substances: β-propiolactone, cetrimonium bromide (CTAB) and polysorbate 80.

Optaflu is prepared from virus propagated in MDCK cells, a continuous cell line. These cells were adapted to grow freely in suspension in culture medium. The virus is inactivated with ß-propiolactone, disrupted by the detergent cetyltrimethylammonium bromide and purified through several process steps. Each of the 3 virus strains is produced and purified separately then pooled to formulate the trivalent vaccine. The manufacturing process for this product does not use eggs.

PHARMACOLOGY

Optaflu induces humoral antibodies against haemagglutinins, the surface antigens of the virus. These antibodies neutralise influenza viruses and are important in the prevention of natural infections.

Seroprotection is generally obtained within 3 weeks, as shown by the pivotal phase III clinical study V58P4 for the adult population. The duration of postvaccinal immunity to homologous strains or to strains closely related to the vaccine strains varies but is usually 6-12 months.

CLINICAL TRIALS

Efficacy

A multinational (US, Finland, and Poland), randomised, observer-blinded, placebo-controlled trial (V58P13) was performed to assess clinical efficacy and safety of Optaflu during the 2007-2008 influenza season in adults aged 18 to 49 years. A total of 11,404 participants were enrolled to receive Optaflu (N=3828), Agrippal (N=3676) or placebo (N=3900) in a 1:1:1 ratio. Among the overall study population enrolled, the mean age was 33 years, 55% were female, 84% were Caucasian, 7% were Black, 7% were Hispanic, and 2% were of other ethnic origin.

Optaflu efficacy was defined as the prevention of culture-confirmed symptomatic influenza illness

caused by viruses antigenically matched to those in the vaccine compared to placebo. Influenza cases were identified by active and passive surveillance of influenza-like illness (ILI). ILI was defined as fever (oral temperature ≥38°C) and cough or sore throat. After an episode of ILI, nose and throat swab samples were collected for analysis. Overall vaccine efficacy against all influenza viral subtypes and vaccine efficacy against individual influenza viral subtypes were calculated (Tables 1 and 2, respectively).

The vaccine was to be considered statistically compliant with the May 2007 CBER Guidance for Industry criteria for estimating VE against placebo if the lower limit of the one-sided simultaneous 97.5% Confidence Interval (CI) for the estimate of VE relative to placebo was greater than 40%.

Table 1: Vaccine Efficacy against Culture-Confirmed Influenza

	Number of participants per protocol	Number of participants with influenza	Attack Rate (%)	Vaccine Efficacy*	
				%	Lower Limit of One- Sided 97.5% CI
Antigenically Matched Strains					
Optaflu	3776	7	0.19	83.	61.0
Placebo	3843	44	1.14	--	--

*Simultaneous one-sided 97.5% confidence intervals for the vaccine efficacy of each influenza vaccine relative to placebo based on the Sidak-corrected score confidence intervals for the two relative risks. Vaccine Efficacy = (1 - Relative Risk) x 100 %

Table 2: Comparative Efficacy of Optaflu versus Placebo against Culture-Confirmed Influenza by Influenza Viral Subtype

	Optaflu (N=3776)		Placebo (N=3843)		Vaccine Efficacy*	
	Attack Rate (%)	Number of Participants with Influenza	Attack Rate	Number of Participants with Influenza	%	Lower Limit of One-Sided 97.5% CI
Antigenically Matched Strains						
A/H3N2**	0. 05	2	0	0	--	--
A/H1N1	0.13	5	1.12	43	88.2	67.4
B**	0	0	0.03	1	--	--

* Simultaneous one-sided 97.5% confidence intervals for the vaccine efficacy of each influenza vaccine relative to placebo based on the Sidak-corrected score confidence intervals for the two relative risks. Vaccine Efficacy = (1 - Relative Risk) x 100 %;

** There were too few cases of influenza due to vaccine-matched influenza A/H3N2 or B to adequately assess vaccine efficacy.

Immunogenicity in Adults 18 to 64 Years of Age

In all randomised, controlled clinical studies with Optaflu, immune responses measured by haemagglutination inhibition (HI) antibody titres to each virus strain in the vaccine were evaluated in sera obtained 21 days after administration of Optaflu.

These studies included the efficacy study performed in 2007-2008 in the US, Finland and Poland (V58P13), in which immunogenicity was evaluated in a subset of participants, consisting of the first 1045 participants enrolled and randomised in the US sites. Among the overall study population enrolled, 58% were female and the distribution of all participants was 67% Caucasian, 20% Hispanic, 11% Black, 1% Asian and 1% of other ethnic origin. The participants' age ranged between 18 and 49 years (mean age of 33 years old).

In the clinical study conducted in Poland in 2004-2005(V58P4), immunogenicity data were obtained from 1655 participants (818 and 837 for Optaflu and Agrippal, respectively). Among the

overall study population enrolled, 59% were female and 100% of participants were Caucasian. The participants' age ranged between 18 and 64 years (mean age of 43.6 years).

In the clinical study conducted in US in 2005-2006 (V58P5), immunogenicity data were obtained from 610 participants (307 and 303 for Optaflu and Fluvirin, respectively). Among the overall study population enrolled, 64% were female, and the distribution of participants by ethnicity was 96% Caucasian, 2% African American, 1% Hispanic and <1% Asian. The participants' age ranged between 18 and 49 years (mean age of 33.9 years).

In the clinical study conducted in Lithuania in 2005-2006 (V58P9), participants were randomly assigned at a 2:2:2:1 ratio to receive either one of three consecutive Optaflu lots or Agrippal used for comparison of the safety profile. Immunogenicity data were obtained from a total of 1185 participants (1017 and 168 for Optaflu and Agrippal, respectively). Among the overall study population enrolled, 61% were female, and 100% of participants were Caucasian. The participants' age ranged between 18 and 60 years (mean age of 32.5 years).

In all of the studies used for assessment of Optaflu immunogenicity, analysis of the following co-primary endpoints were performed for each antigen contained in the vaccine: 1) assessment of the lower bound of the two-sided 95% confidence intervals (CI) for the percentage of participants with HI antibody titres ≥ 40 after vaccination, and 2) assessment of the lower bounds of the two-sided 95% CIs for percentages of participants with seroconversion (defined as percentage of participants with either a pre-vaccination HI titre <1:10 and a post-vaccination HI titre > 1:40 or a pre-vaccination HI titre > 1:10 and at least a four-fold rise in post-vaccination HI antibody titre). The pre-specified targets followed the U.S. Center for Biological Evaluation and Research (CBER) criteria: endpoint 1) 70% for adults 18-64 years of age and 60% for those 65 years of age and older, and endpoint 2) 40% for adults 18-64 years of age and 30% for those 65 years of age and older.

Table 3: Immunogenicity in Adults 18-64 Years of Age

Study	**Vaccine strain**	**% HI Titre ≥1:40**	**% Seroconversion** (95% CI %)**
V58P4 N=818	A/H1N1	90 (87-92)	66 (63-70)
	A/H3N2	99 (98-99)	64 (61-68)
	B	90 (88-92)	83 (81-86)
V58P5 N=307	A/H1N1	96 (94-98)	62 (57-68)
	A/H3N2	91 (87-94)	85 (81-89)
	B	94 (91-96)	77 (72-81)
V58P9 N=1017*	A/H1N1	94 (92-95)	81 (79-84)
	A/H3N2	93 (91-95)	83 (80-85)
	B	91 (89-93)	78 (76-81)
V58P13 N=228	A/H1N1	99 (97-100)	78 (72-83)
	A/H3N2	99 (98-100)	59 (53-66)
	B	78 (72-83)	51 (45-58)

* *Pooled number of participants receiving one of the three manufacturing lots of Agrippal*

** *Rates of seroconversion = percentage of participants with either a pre-vaccination HI titre < 1:10 and a post-vaccination HI titre > 1:40 or a pre-vaccination HI titre > 1:10 and at least a four-fold rise in post-vaccination HI antibody titre*

Immunogenicity in Adults 65 Years of Age and Older

In the clinical study conducted in Poland in 2004-2005, 985 participants (504 and 481 for Optaflu and Agrippal, respectively) were evaluated. Among the overall study population enrolled, 56% were female, and 100% of participants were Caucasian. The mean age of the study participants was 71.3 years.

Table 4: Immunogenicity in Adults 65 Years of Age and Older

Study	Vaccine strain	% HI Titre ≥1:40	% Seroconversion* (95% CI %)
V58P4 N=504	A/H1N1	86 (83-89)	55 (50-59)
	A/H3N2	97 (95-98)	68 (64-72)
	B	90 (87-93)	80 (76-84)

**Rates of seroconversion = percentage of participants with either a pre-vaccination HI titre < 1:10 and a post-vaccination HI titre > 1:40 or a pre-vaccination HI titre > 1:10 and at least a four-fold rise in post-vaccination HI antibody titre.*

Non-inferiority in Adults

In study (V58P4), non-inferiority of Optaflu to Agrippal was demonstrated for HI antibody responses to all three strains for both post-vaccination geometric mean titre (GMT) ratios and seroconversion rates (i.e. the lower limit of the two-sided 95% CI for the ratio of the GMTs (Optaflu /Agrippal) was >0.67; and the lower limit of the two-sided 95% CI for the difference between the seroconversion rates (Optaflu and Agrippal) was >-10%). Non-inferiority of Optaflu was demonstrated in both age groups evaluated (adults 18 through 60 years and adults > 60 years of age, Table 5).

Table 5: Non-inferiority Analysis of Optaflu to a licensed Comparator in Adults 18 Through 60 Years and > 60 Years of Age (Study V58P4)

	Vaccine Group Ratio/Difference (95% CI) Optaflu Versus Comparator*		
	A/H1N1	**A/H3N2**	**B**
Participants 18 through 60 years			
GMTs ratio (Optaflu / Agrippal)	1.07 (0.9, 1.28)	0.85 (0.72, 0.99)	1.14 (0.99, 1.3)
Difference in Seroconversion Rates** (Optaflu – Agrippal)	2% (-3, 7)	-1% (-6, 4)	4% (0, 8)
Participants > 60 Years			
GMTs ratio (Optaflu / Agrippal)	0.96 (0.82, 1.12)	0.87 (0.74, 1.02)	1.27 (1.11, 1.46)
Difference in Seroconversion Rates** (Optaflu – Agrippal)	0% (-6, 5)	3% (-2, 8)	6% (2, 11)

* Agrippal

**Rates of seroconversion = percentage of participants with either a pre-vaccination HI titre < 1:10 and a post-vaccination HI titre > 1:40 or a pre-vaccination HI titre > 1:10 and at least a four-fold rise in post-vaccination HI antibody titre

In addition, in the study conducted in the US in 2005-2006 (V58P5), non-inferiority of Optaflu in adults 18 to < 50 years of age was demonstrated for all three influenza strains, after post hoc adjustment for baseline imbalances in titre and by centre. Non-inferiority was based on comparison of post-vaccination GMT ratios between Optaflu and control vaccine as measured by egg antigen-derived assay according to protocol-specified criteria: (i.e. the lower limit of the two-sided 95% CI for the ratio of the GMTs (Optaflu / Fluvirin) was >0.5).

INDICATIONS

For the prevention of influenza caused by Influenza Virus, Types A and B in adults over 18 years of age.

For full details regarding the recommendations for influenza vaccination refer to the current Australian Immunisation Handbook.

CONTRAINDICATIONS

Hypersensitivity to the active substances, to any of the excipients or to residues from the manufacturing process.

The vaccine may contain residues of the following substances: cetrimonium bromide (CTAB) bromide, polysorbate 80 and β-propiolactone.

Immunisation should be postponed in patients with an acute severe febrile illness (fever >38.5°C). The presence of a minor illness with or without fever should not contraindicate use of Optaflu.

PRECAUTIONS

As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of a rare anaphylactic event following the administration of the vaccine.

Optaflu should under no circumstances be administered intravascularly.

Anxiety-related reactions, including vasovagal reactions (syncope), hyperventilation or stress-related reactions, may occur in association with vaccination as a psychogenic response to the needle injection (see section ADVERSE EFFECTS). It is important that procedures are in place to avoid injury from fainting.

Antibody response in patients with endogenous or iatrogenic immunosuppression may be insufficient.

A protective immune response may not be elicited in all vaccinees. As with all infectious disease vaccines, timely administration before and minimisation of risk of exposure is best to avoid onset of disease.

Latex-sensitive individuals: Although no natural rubber latex is detected in the syringe tip cap, the safe use of Optaflu in latex-sensitive individuals has not been established.

Patients with a history of Guillain-Barré Syndrome have a substantially greater likelihood of subsequently experiencing GBS than people without such a history. Thus, the likelihood of coincidentally experiencing GBS after influenza vaccination is expected to be greater in these patients than among people with no history of this syndrome. Whether influenza vaccination specifically might increase the risk for recurrence of GBS is unknown.

If GBS has occurred within 6 weeks of receipt of prior influenza vaccine, the decision to give Optaflu or any influenza vaccine should be based on careful evaluation of the potential benefits and possible risks.

Following influenza vaccination, false-positive serology test results may be obtained by the ELISA method for antibody to human immunodeficiency virus-1 (HIV-1), hepatitis C virus and, especially, HTLV-1. In such cases, the Western blot method is negative. These transitory false-positive results may be due to IgM production in response to the vaccine.

Effects on Fertility

There were no effects on the mating performance or fertility of female rabbits in a reproductive and developmental toxicity study in which rabbits were intramuscularly injected with the clinical dose of Optaflu 3 times prior to mating and twice during gestation. Effects on male fertility have not been assessed in animals.

Carcinogenicity and genotoxicity

Optaflu has not been tested for carcinogenic or genotoxic potential.

Use in Pregnancy

Category B1.

The safety of Optaflu in pregnancy and breast-feeding has not been assessed in clinical trials. Healthcare providers should assess the benefit and potential risks of administering the vaccine to pregnant women taking into consideration official recommendations. Refer to the current edition of The Australian Immunisation Handbook for recommendations for use in pregnancy.

In general data from influenza vaccinations in pregnant women do not indicate adverse foetal and maternal outcomes attributable to the vaccine. .

In a reproductive and developmental toxicity study, the effect of Optaflu on embryofoetal and postnatal development was evaluated in pregnant rabbits. Female rabbits were administered the clinical dose of Optaflu by intramuscular injection 3 times prior to mating and on gestation days 7 and 20. There were no adverse effects on female mating or fertility, pregnancy, embryofoetal development or postnatal development. Anti-influenza antibodies were detected in all treated rabbits and their kits.

Use in Lactation

There is no human data on use during lactation.

In an embryofoetal and postnatal development study in rabbits, maternal treatment prior to mating and during gestation had no effects on kit development, assessed to lactation day 29 (see also Use in Pregnancy).

Genotoxicity

Optaflu has not been evaluated for genotoxic potential.

Carcinogenicity

Optaflu has not been evaluated for carcinogenic potential.

Paediatric use

The safety and efficacy of Optaflu in children and adolescents less than 18 years of age have not yet been established. Therefore, Optaflu is not recommended for use in children and adolescents.

INTERACTIONS WITH OTHER MEDICINES

There are limited data on co-administration of Optaflu with other vaccines.

If Optaflu is to be given at the same time as another injectable vaccine(s), the vaccine(s) should always be administered to separate limbs. It should be noted that adverse reactions may be intensified.

The immunological response and vaccine efficacy may be diminished if the patient is undergoing immunosuppressant treatment.

Elderly patients on long-term warfarin therapy may experience an increase of International Normalised Ratio (INR) after influenza vaccination. Therefore more frequent monitoring for six weeks after receiving influenza vaccine may be advisable.

ADVERSE EFFECTS

Adverse reactions from clinical trials

The safety profile of Optaflu was evaluated in six randomised, controlled studies including 6138 adults 18 through 64 years of age and 572 participants greater than 65 years of age. In these studies, influenza vaccines (Fluvirin® or Agrippal®) or placebo were used as comparators.

In all studies, solicited local injection site and systemic reactions were collected from participants who completed a symptom diary card for 7 days following vaccination. These reactions were selected based on the usual safety profile of inactivated influenza vaccines such as Fluvirin and Agrippal.

Adults 18 to 64 years of age

Solicited adverse reactions in the pooled safety population of adults 18 through 64 years of age are shown in Table 7 (N=6138 for Optaflu). Overall, the most commonly (≥ 1/10) solicited AEs occurring in adults within 7 days of vaccination with Optaflu were pain at the injection site, erythema at the injection site, headache, fatigue, myalgia and malaise. In general, participants in both the Optaflu and comparator vaccine groups reported similar percentages of solicited AEs. Mild and transient injection site pain was reported more frequently in the Optaflu group. Rates of unsolicited adverse events and serious adverse events were comparable between participants who received Optaflu and comparator vaccines.

Adults 65 Years of Age and Older

Solicited AEs in the pooled safety population of adults ≥ 65 years of age are shown in below Table 7 (N=572 for Optaflu). Overall, the most common (≥1/10) solicited AEs occurring within 7 days of vaccination were injection site erythema, fatigue, headache and malaise. Participants in both the Optaflu and comparator vaccine groups reported similar percentages of solicited AEs. Rates of unsolicited adverse events and serious adverse events were comparable between participants who received Optaflu and comparator vaccines.

Table 7: Adverse Reactions Reported from Clinical Trials in the Adult Populations after Vaccination with Optaflu.

System Organ Class	Optaflu		Placebo[1] *
	Adults 18-64 Years	Adults≥ 65 Years	
	N=6138	N=572	Adults 18-49 Years N= 3894
	Frequency category**	Frequency category**	Frequency category**
Blood and lymphatic system disorders			
Lymphadenopathy	Uncommon	Uncommon	Uncommon
Nervous system disorders			
Headache	Very common	Very common	Very common
Skin and subcutaneous tissue disorders			
Sweating	Common	Common	Common
Musculoskeletal and connective tissue disorders			
Myalgia	Very common	Common	Common
Arthralgia	Common	Common	Common
General disorders and administration site conditions			
Injection site pain	Very common	Common	Very common
Erythema	Very common	Very common	Very common
Fatigue	Very common	Very common	Very common
Malaise	Very common	Very common	Common
Induration	Common	Common	Common
Swelling	Common	Common	Common
Ecchymosis	Common	Common	Common
Chills	Common	Common	Common
Fever (≥38° C)	Common	Uncommon	Uncommon

*Phosphate buffered saline
**Frequency category definitions: Very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100) Rare (≥1/10,000 - <1/1,000); Very Rare (<1/10,000); Not known (cannot be estimated from the available data)[1] Data represented are based on a single study that enrolled adult subjects 18-49 years of age.

Adverse reactions from post-marketing spontaneous reports

The following adverse events have been identified during post-approval use of Optaflu. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish, for all events, a causal relationship to vaccine exposure.

Nervous systems disorders:

Syncope, presyncope

General disorders and administration site conditions:

Extensive swelling of injected limb

Immune system disorders:

Anaphylactic reaction, angioedema

Skin and subcutaneous tissue disorders:

Generalised skin reactions including pruritus, urticaria or non-specific rash

Currently, more than 15,750 subjects have been exposed to OPTAFLU in clinical trials, and more than 4.5 million patients have received this vaccine in the post-marketing setting. As of 31 December 2014, no OPTAFLU-confirmed reports of encephalitis, Guillain-Barré syndrome, neuritis, vasculitis, thrombocytopenia, or allergic reactions leading to shock have been received. These specific complications have occurred after vaccination with egg-based influenza vaccines at low rates, but their relationship to the method of production (ie egg or cell) is unclear.

DOSAGE AND ADMINISTRATION

Dosage:

Adult 18 years of age and older: a single 0.5 mL dose

Administration:

Immunisation should be carried out by intramuscular injection into the deltoid muscle. Optaflu should under no circumstances be administered intravascularly.

Allow the vaccine to reach room temperature before use.

Shake before use. After shaking, the normal appearance of the vaccine is a clear to slightly opalescent suspension.

Visually inspect the contents of each pre-filled syringe for particulate matter and/or change in colour prior to administration. If either condition exists, do not administer the vaccine.

Do not use the vaccine if it has not been stored at the appropriate temperature (between 2°C to 8°C).

Product is for single use in one patient only. Discard any residue.

Any unused product or waste material should be disposed of in compliance with local requirements.

OVERDOSAGE

There is no experience with overdosage with Optaflu. For general advice on overdose management in Australia, contact the Poisons Information Centre on 13 11 26.

PRESENTATION AND STORAGE CONDITIONS

Presentation

Each pre-filled syringe (type I glass) contains a 0.5 mL dose of vaccine. Packs of 1 with needle (AUST R 220737) or packs of 1 and 10 without needle (AUST R 220736).
Not all pack size and presentations may be marketed.

Storage conditions

Store refrigerated between 2°C to 8°C. Do not freeze. Store in the original package in order to protect from light.

NAME AND ADDRESS OF THE SPONSOR

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NSW 2113

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POISON SCHEDULE OF THE MEDICINE

All states and ACT: S4

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (the ARTG)

13 March 2015

Product Information (PI) and Consumer Medicine Information (CMI) documents are regularly updated.
Please also refer to the TGA web site (https://www.ebs.tga.gov.au) for the most up to date PI and CMI.

For medical enquiries please contact 1800 671 203 (phone) or medinfo.phauno@novartis.com (email)

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