PANVAX® HxNy Pandemic Influenza Vaccine

NAME OF THE MEDICINE

Pandemic influenza vaccine (split virion, inactivated and adjuvanted), suspension for injection containing influenza virus haemagglutinin as the active ingredient.

QUALITATIVE AND QUANTITATIVE COMPOSITION

The vaccine is a purified, inactivated, monovalent, split virion (split virus), adjuvanted vaccine containing antigen of the following type:

A/Official strain (HxNy)-like (A/HxNy Official strain)

30 mcg HA per 0.5 mL dose

PANVAX® vaccine is prepared from influenza virus propagated in the allantoic fluid of embryonated chicken eggs. The virus is harvested from the eggs, purified, inactivated with beta-propiolactone and disrupted with sodium taurodeoxycholate to produce split virion particles which are further purified prior to formulation with aluminium phosphate adjuvant. For a full list of excipients, see section **List of excipients**.

Each dose may also contain sodium taurodeoxycholate, ovalbumin, sucrose, neomycin, polymyxin B sulfate and beta-propiolactone.

PHARMACEUTICAL FORM

PANVAX® is a suspension for injection. It is a homogenous creamy/white opaque liquid suspension with no large visible clumps.

CLINICAL PARTICULARS

Therapeutic indications

Prophylaxis of influenza in an officially declared pandemic situation. Pandemic influenza vaccine should be used in accordance with Singaporean Health Authorities' recommendations, taking into account the recommendation of the World Health Organisation.

Dosage and method of administration

Dose

Two 0.5 mL doses, 21 days apart.

Method of administration

The vaccine should be administered by intramuscular injection.

The vaccine should be allowed to reach room temperature before use. Shake before use. The vaccine should appear as a homogeneous creamy/white opaque liquid suspension with no large clumps visible.

Once opened, the vaccine is to be used immediately and within the one vaccination session, with any remaining contents discarded in accordance with local requirements. No additions should be made to the contents of the vial.

Instructions for use and handling

It is important that the contents of the container be shaken thoroughly immediately before use. The vaccine should appear as a homogenous creamy/white opaque liquid suspension with no large clumps visible.

Contraindications

History of an anaphylactic (i.e. life-threatening) reaction to any of the constituents or trace residues (e.g. eggs, chicken protein refer to sections **Qualitative and Quantitative Composition** and **List of excipients**) of this vaccine. However, in a pandemic situation, it may be appropriate to give the vaccine, provided that facilities for resuscitation are immediately available in case of need.

Special warnings and precautions for use

As with all injectable vaccines, appropriate medical treatment and supervision should always be available to manage the rare event of an anaphylactic reaction following administration of the vaccine.

Caution is needed when administering this vaccine to persons with a known hypersensitivity (other than anaphylactic reaction, see section **Contraindications**) to the active substance, to any of the excipients, to thiomersal and to residues e.g. eggs, chicken protein, neomycin or polymyxin B sulfate.

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

If the pandemic situation allows, immunisation shall be postponed in patients with severe febrile illness or acute infection.

PANVAX® vaccine should under no circumstances be administered intravascularly.

Use in the elderly

Refer to sections **ADVERSE EFFECTS (UNDESIRABLE EFFECTS) – Clinical trials (Adults)** and **PHARMACODYNAMIC PROPERTIES - Clinical trials** for elderly data.

Paediatric use

PANVAX® vaccine may be used in children from 6 months of age (refer to sections **ADVERSE EFFECTS (UNDESIRABLE EFFECTS) - Clinical trial (Paediatric)** and **PHARMACODYNAMIC PROPERTIES - Clinical trials**.

Interactions with other medicines and other forms of interactions

The vaccine should not be mixed with other injection fluids.

PANVAX® vaccine should not be given at the same time as other vaccines. However, if co-administration with another vaccine is indicated, immunisation should be carried out on separate limbs. It should be noted that the adverse reactions may be intensified.

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

Influenza vaccines may impair the metabolism of warfarin, theophylline, phenytoin, phenobarbitone and carbamazepine by the hepatic P450 system. Results from studies showed conflicting evidence or found no evidence of an interaction. Studies which found a positive association have been variable in the degree of interaction and time after vaccination for the interaction to take effect. The interaction may be idiosyncratic.

Fertility, pregnancy and lactation

Effects on fertility

No data available.

Use in pregnancy (Category B2)

The effects of PANVAX® vaccine have not been studied in pregnant women. Therefore, health care providers should assess the risks and potential benefits of administering the vaccine to pregnant women on a case by case basis, taking into account Singaporean Health Authorities' recommendations. Data from vaccinations with inter-pandemic trivalent vaccines in pregnant women do not indicate that adverse foetal and maternal outcomes were attributable to the vaccine. Animal embryofoetal development studies have not been conducted with the vaccine.

Use in lactation

PANVAX® vaccine may be used during lactation.

Effects on ability to drive and use machines

The vaccine is unlikely to have an effect on the ability to drive and use machines.

ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical trials (Adults)

Adverse reactions from the three clinical trials in adults 18 years and older with prototype pandemic vaccines (A/Vietnam/1194/2004; H5N1) are listed below (see Pharmacology for more information on the prototype vaccines). A total of 801 adult participants received the inactivated, split virion, monovalent, aluminium-adjuvanted vaccine with different influenza HA antigen doses of 7.5 μg, 15 μg, 30 μg and 45 μg.

The frequency of adverse reactions observed in participants > 65 years was lower compared to those in the 18 to 64 year age group.

Adverse effects are listed according to the following frequency: Very Common (≥1/10), Common (≥ 1/100 to < 1/10), Uncommon (≥ 1/1,000 to < 1/100), Rare (≥ 1/10,000 to < 1/1,000), Very Rare (< 1/10,000)

Infections and Infestations
Common - nasopharyngitis, upper respiratory tract infection

Nervous System Disorders
Very Common - headache

Respiratory, Thoracic and Mediastinal Disorders
Common - cough, nasal congestion, pharyngolaryngeal pain, rhinorrhoea

Gastrointestinal Disorders
Very Common - nausea
Common - diarrhoea, toothache, vomiting

Skin and Subcutaneous Tissue Disorders
Common – hyperhidrosis

Musculoskeletal and Connective Tissue Disorders
Very Common - myalgia
Common - arthralgia, back pain

Reproductive System and Breast Disorders
Common - dysmenorrhoea

General Disorders and Administration Site Conditions
Very Common - fatigue, injection site erythema, injection site induration, injection site pain, injection site swelling
Common - chills, injection site haemorrhage, pyrexia

These reactions generally resolve within 3 days.

Clinical trial (Paediatric)

Adverse reactions from the Paediatric clinical trial, in children aged 6 months to < 9 years, are listed below. The safety population consisted of a total of 149 participants who received the inactivated, split virion, monovalent, aluminium-adjuvanted vaccine with 30 μg or 45 μg HA influenza antigen per dose.

Infections and Infestations
Common - upper respiratory tract infection, gastroenteritis, otitis media

Metabolism and Nutritional Disorders
Very common – decreased appetite

Nervous System Disorders
Very Common – headache

Eye Disorders
Common – conjunctivitis

Ear and Labyrinth Disorders
Common – ear pain

Respiratory, Thoracic and Mediastinal Disorders
Very common – rhinorrhoea, wheezing
Common – asthma, cough, pharyngolaryngeal pain

Gastrointestinal Disorders
Very Common – diarrhoea, vomiting
Common – abdominal pain

Skin and Subcutaneous Tissue Disorders
Common – rash

Musculoskeletal and Connective Tissue Disorders
Very Common - myalgia

General Disorders and Administration Site Conditions
Very Common - injection site pain, injection site erythema, injection site induration, injection site haemorrhage, injection site swelling, irritability, pyrexia

These reactions generally resolve within 3 days.

Injection site reactions occurred slightly less frequently in Group A (≥ 6 months to < 3 years) compared to Group B (≥ 3 years to < 9 years). Headache and myalgia was reported less frequently in Group A, while fever, irritability, reduced appetite, diarrhoea, wheezing and vomiting occurred less frequently in the Group B population.

Post-marketing surveillance

Post-marketing information is not available for PANVAX® vaccine, however similar adverse reactions to inter-pandemic trivalent influenza vaccines may be observed. From post marketing surveillance with inter-pandemic trivalent influenza vaccines, the following adverse reactions have been reported:

Uncommon (≥ 1/1,000 to < 1/100):
Generalised skin reactions including pruritus, urticaria or non-specific rash.

Rare (≥ 1/10,000 to < 1/1000):
Neuralgia, paraesthesia, convulsions, transient thrombocytopenia. Allergic reactions, in rare cases leading to shock, have been reported.

Very rare (< 1/10,000):
Vasculitis with transient renal involvement.
Neurological disorders, such as encephalomyelitis, neuritis and Guillain Barré syndrome.

This medicinal product contains thiomersal (an organomercuric compound) as a preservative, and therefore, it is possible that sensitisation reactions may occur.

OVERDOSAGE

There is no specific information on overdose of PANVAX® vaccine.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Mechanism of action

Prototype pandemic influenza vaccines contain influenza virus antigens that are different from those included in seasonal trivalent influenza vaccines and may also be substantially different from the virus which causes pandemic influenza. If a pandemic influenza virus emerges, the clinical efficacy and safety data obtained from clinical trials with prototype pandemic influenza vaccines are expected to be relevant for the pandemic vaccine made from the official pandemic influenza virus strain.

Clinical experience with prototype pandemic vaccines, following a two-dose primary vaccination course, has been derived from clinical trials in healthy adult, older adult and paediatric populations. The efficacy of prototype pandemic vaccines is assessed by serum immunogenicity, since clinical protection is not able to be evaluated.

The immunogenicity of prototype vaccines has been assessed in clinical trials by two serum antibody assays, the haemagglutination inhibition (HI) assay and a viral microneutralisation (MN) assay. There are currently no defined levels of serum antibody responses known to correlate with clinical protection against infection with pandemic influenza viruses. Guidelines for assessment of the pandemic influenza vaccines are based on those for inter-pandemic influenza vaccines developed by the EuropeanMedicines Agency (EMEA) *Note for Guidance on Harmonisation of Requirements for Influenza Vaccines* (CPMP/BWP/214/96) and the EMEA guidance document for pandemic vaccines (CPMP/VEG/4717/03).

A ferret efficacy challenge study using the prototype A/Vietnam/1194/2004 (H5N1) pandemic influenza vaccine has demonstrated that seroconversion (as measured by both HI and MN immune responses) in ferrets vaccinated with the 30 μg HA per dose adjuvanted formulation was associated with 100% survival following lethal challenge and also prevented serious morbidity. This data provides support for the assessment of HI and MN immune responses as a surrogate measure of clinical efficacy in human clinical trials.

Clinical trials

Four clinical trials have been conducted to assess the immunogenicity and safety of a prototype pandemic influenza vaccine in healthy persons aged 6 months and older.

The safety of the vaccine was assessed in 4 randomised Phase I or Phase II studies conducted in persons aged 6 months and older. A Phase I trial in 400 adults, 18 to 45 years of age, assessed vaccines formulated with lower HA antigen doses, with and without aluminium phosphate adjuvant. The data from this study demonstrated that higher antigen doses and an

adjuvant were required, and that two doses of the vaccine elicited modest levels of cross-reactive neutralising antibodies against antigenically distinct H5N1 strains. The immunogenicity data from this study are not presented; however the safety data has been included in the overall safety analysis for the vaccine.

Three double blind, randomised Phase II clinical studies evaluated the immunogenicity of an inactivated, split virion, monovalent, aluminium phosphate-adjuvanted, prototype pandemic vaccine in adults aged 18 to 64 years, elderly adults aged 65 years and over, and children aged 6 months to less than 9 years. Two vaccinations were administered 21 days apart.

For the Adult Phase II study, immunogenicity was assessed by HI and MN approximately 21 days after each vaccination and by MN only 6 months after the second vaccination to evaluate antibody persistence. For the older adults and paediatric studies, immunogenicity was assessed by MN only approximately 21 days after each vaccination and 6 months after the second vaccination.

The Adult Phase II study enrolled 400 participants, aged 18 to 64 years. Immunogenicity results for the 30 μg HA per dose vaccine are shown in Tables 1a and 1b.

Table 1a: Immunogenicity (HI)Results for Adult Population (18 to 64 yrs)

Serum HI antibody	After Dose 1 n=200 (95% CI)	After Dose 2 n=197 (95% CI)
Fold increase in GMT[a]	2.8 (2.3,3.5)	6.8 (5.5,8.4)
Seroconversion or significant increase[b]	22.0% (16.5,28.4)	48.2% (41.1,55.4)
Proportion with HI ≥ 40	23.0% (17.4,29.5)	49.7% (42.6,56.9)

[a] Fold increase in GMT (geometric mean titre) is the fold increase in antibody titre over the pre-vaccination GMT. [b] [b]'Seroconversion or significant increase' is defined as at least a four fold increase over the pre- vaccination GMT, and with a post-vaccination titre value of at least 40.

Table 1b: Immunogenicity (MN) Results for Adult Population (18 to 64 yrs)

Serum viral neutralising antibody (MN)	After Dose 1 n=200 (95% CI)	After Dose 2 n=197 (95% CI)	6 months after Dose 2 n=192 (95% CI)
Fold increase in GMT[a]	1.8 (1.5,2.0)	4.3 (3.7,5.0)	3.4 (2.9,4.1)
Seroconversion or significant increase[b]	18.5% (13.4,24.6)	53.8% (46.6,60.9)	40.4% (33.4,47.7)
Proportion seropositive (MN ≥ 20)	28.0% (21.9,34.8)	72.6% (65.8,78.7)	60.1% (52.8,67.1)
Proportion with MN ≥ 40	18.5% (13.4,24.6)	53.8% (46.6,60.9)	40.4% (33.4,47.7)

The Older Adult Phase II study enrolled 201 participants, 65 years of age and older.

Immunogenicity results for the 30 µg HA per dose vaccine are shown in Table 2.

Table 2: Immunogenicity (MN) Results for Older Adult Population (>65 yrs)

Serum viral neutralising antibody (MN)	After Dose 1 n=100 (95% CI)	After Dose 2 n=101 (95% CI)	6 months after Dose 2 n=98 (95% CI)
Fold increase in GMT[a]	2.1 (1.6,2.7)	4.2 (3.2,5.4)	2.8 (2.2,3.5)
Seroconversion or significant increase[b]	22.0% (14.3,31.4)	47.5% (37.5,57.7)	38.8% (29.1,49.2)
Proportion seropositive (MN ≥ 20)	32.0% (23.0,42.1)	62.4% (52.2,71.8)	51.0% (40.7,61.3)
Proportion with MN ≥ 40	24.0% (16.0,33.6)	48.5% (38.4,58.7)	40.8% (31.0,51.2)

The Paediatric Phase II study enrolled 150 participants, aged 6 months to less than 9 years. Participants within this study were further defined into two age groups: Group A, 6 months to less than 3 years, and Group B, 3 years to less than 9 years. Immunogenicity results were comparable across these age groups and are presented for the 30 µg HA per dose vaccine as combined results in Table 3.

Table 3: Immunogenicity (MN) Results for Paediatric Population (6 months to less than 9 yrs)

Serum viral neutralising antibody (MN)	After Dose 1 n=55 (95% CI)	After Dose 2 n=66 (95% CI)	6 months after Dose 2 n=67 (95% CI)
Fold increase in GMT [a, 1]	1.6 (1.2, 2.2)	40.2 (30.6, 52.8)	5.4 (4.3, 6.8)
Seroconversion or significant increase [b, 1]	12.7% (5.3, 24.5)	98.3% (91.1, 100.0)	66.7% (53.3, 78.3)
Proportion seropositive (MN ≥ 20)	25.5% (14.7, 39.0)	98.5% (91.8, 100.0)	85.1% (74.3, 92.6)
Proportion with MN ≥ 40	14.5% (6.5, 26.7)	98.5% (91.8, 100.0)	67.2% (54.6, 78.2)

[1] The number of participants assessed for Fold Increase in GMT and Seroconversion or significant increase, after Dose 2 and 6 months after Dose 2, was 60.

Pharmacokinetic properties

Not applicable.

Preclinical safety data

Genotoxicity

No data available.

Carcinogenicity

No data available.

PHARMACEUTICAL PARTICULARS

List of excipients

Each 0.5 mL dose of PANVAX® also contains nominally:

Table 4: List of excipients

Sodium chloride	4.1 milligram
Dibasic sodium phosphate	3.0 milligram
Monobasic sodium phosphate - anhydrous	12 microgram
Potassium chloride	10 microgram
Potassium phosphate - monobasic	10 microgram
Calcium chloride	0.2 microgram
Thiomersal	0.01% w/v
Water for injections	Up to 0.5 mL

Table 5: Adjuvants

Aluminium (as Aluminium Phosphate Adjuvant)	0.5 milligram

Incompatibilities

Incompatibilities were either not assessed or identified as part of the registration of the medicine.

Shelf life

The shelf life of the vaccine is 24 months when stored at +2°C to +8°C. The expiry date is indicated on the container label.

Special precautions for storage

PANVAX® vaccine should be stored, protected from light at 2°C to 8°C. IT MUST NOT BE FROZEN. Store in the original package in order to protect from light.

Nature and contents of container

Multi-dose Vial

Multi-dose type 1 glass vial containing 10mL of PANVAX®.

The multi-dose vial is closed with a latex-free stopper and sealed with an aluminium crimp seal. The aluminium seal has attached a plastic tear-away cap that is removed to gain access to the vial closure. The cap is present to protect the vial closure and to indicate if the vial has been tampered with. Once removed, the cap cannot be re-affixed to the vial. Vials are packed into a cardboard carton (pack size 50), with the approved package insert.

Manufactured by

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