

DATA SHEET
PANDEMRIX™
Pandemic influenza vaccine (split virion, inactivated, AS03 adjuvanted)

NAME OF THE MEDICINE

PANDEMRIX, emulsion and suspension for emulsion for injection.

Pandemic influenza vaccine (split virion, inactivated, AS03 adjuvanted).

DESCRIPTION

The antigen composition will be determined depending on the strain for the pandemic influenza that will be recommended by the World Health Organisation (WHO).

Each 0.5mL vaccine dose contains 3.75 micrograms¹ of antigen² of the recommended strain and is adjuvanted with AS03³.

¹haemagglutinin

²propagated in eggs

³The GlaxoSmithKline proprietary AS03 adjuvant system is composed of squalene (10.68 milligrams), DL- α -tocopherol (11.86 milligrams) and polysorbate 80 (4.85 milligrams)

Each 0.5mL vaccine dose also contains the excipients Polysorbate 80, Octoxinol 10, Thiomersal, Sodium Chloride, Disodium hydrogen phosphate, Potassium dihydrogen phosphate, Potassium Chloride and Magnesium chloride. The vaccine may also contain the following residues: egg residues including ovalbumin, gentamicin sulfate, formaldehyde, sucrose and sodium deoxycholate.

CLINICAL PHARMACOLOGY

Clinical Trials

This section describes the clinical experience with the mock-up vaccines following a two-dose administration.

Mock-up vaccines contain influenza antigens that are different from those in the currently circulating influenza viruses. These antigens can be considered as “novel” antigens and simulate a situation where the target population for vaccination is immunologically naïve. Data obtained with the mock-up vaccine will support a vaccination strategy that is likely to be used for the pandemic vaccine: clinical efficacy and safety data obtained with mock-up vaccines are relevant for the pandemic vaccines.

Two clinical studies have evaluated the immunogenicity of the monovalent pandemic influenza A vaccine (H5N1).

A dose finding study tested different haemagglutinin dosages of the vaccine in a vaccine volume of 1 ml, which is twice the vaccine volume of the final formulation. In this study, approximately 200 unprimed subjects aged 18-60 years received the adjuvanted vaccine following a 0, 21 days schedule. Fifty out of these 200 subjects received 3.75 µg HA/AS03, which is the haemagglutinin dosage of the final formulation.

In a consistency study, more than 900 unprimed subjects aged 18-60 years received 3.75 µg HA/AS03 per 0.5 ml, which is the final formulation of the vaccine following a 0, 21 days schedule.

Immune response against vaccine strain:

Twenty-one days after the first and second dose of the vaccine, the seroprotection rate, the seroconversion rate and seroconversion factor for anti-haemagglutinin (anti-HA) antibody in the subjects who had received the final formulation of the vaccine were as follows:

anti-HA antibody	21 days after 1 st dose	21 days after 2 nd dose
Seroprotection rate*†	44.5%	94.3%
Seroconversion rate†	42.5%	93.7%
Seroconversion factor†	4.1	39.8

* anti-HA ≥1:40

† seroprotection rate (i.e. proportion of subjects with HI titre ≥ 1:40); seroconversion rate (i.e. proportion of subjects who were either seronegative at pre-vaccination and have a protective post-vaccination titre of ≥ 1:40, or who were seropositive at pre-vaccination and have a 4-fold increase in titre); seroconversion factor (i.e; ratio of the post-vaccination GMT and the pre-vaccination GMT)

Twenty-one days after administration of the second dose, 96.0% of subjects had a 4-fold increase in serum neutralising antibody titers.

The ability of the vaccine to induce protection against the vaccine strain was assessed non-clinically using a ferret challenge model. Four groups of 6 ferrets were immunized intramuscularly with an AS03 adjuvanted vaccine containing 15, 5, 1.7 or 0.6 µg of HA derived from H5N1/A/Vietnam/1194/04 (NIBRG-14). The two control groups included ferrets immunized with adjuvant alone or phosphate buffered saline solution. Ferrets were vaccinated on days 0 and 21 and challenged intratracheally on day 49 with a lethal dose of H5N1/A/Vietnam/1194/04. Of the animals receiving adjuvanted vaccine, 87 % were protected against the lethal challenge. Viral shedding into the upper respiratory tract was also reduced in vaccinated animals relative to controls, suggesting a reduced risk of viral transmission. In the unadjuvanted control group, as well as in the adjuvant control group, all animals died or had to be euthanized as they were moribund, three to four days after the start of challenge.

Persistence of immunogenicity:

In the dose finding study, persistence of immunogenicity up to 6 months after the second dose was evaluated in the 50 subjects who have received the 3.75 µg HA/AS03 formulation. The seroprotection rate, the seroconversion rate and seroconversion factor for anti-haemagglutinin (anti-HA) antibody at day 180 were respectively 54.0%, 52.0% and 4.4. A 4-fold increase in serum neutralising antibody titers at this time point was observed in 72% of subjects.

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Cross-reactivity:

In both studies, the candidate vaccine showed the ability to induce a cross-reactive immune response against variants of the vaccine strain.

In the dose finding study, the seroprotection rate, seroconversion rate and seroconversion factor against H5N1 drift variants 21 days after the second dose in a subset of subjects were as follows:

anti-HA antibody	A/Indonesia/5/2005 N = 50	A/Anhui/01/2005 N = 20	A/Turkey/Turkey/1/2005 N = 20
Seroprotection rate*†	20.0%	35.0%	60.0%
Seroconversion rate†	20.0%	35.0%	60.0%
Seroconversion factor†	2.0	3.4	4.7

* anti-HA \geq 1:40

† seroprotection rate (i.e. proportion of subjects with HI titre \geq 1:40); seroconversion rate (i.e. proportion of subjects who were either seronegative at pre-vaccination and have a protective post-vaccination titre of \geq 1:40, or who were seropositive at pre-vaccination and have a 4-fold increase in titre); seroconversion factor (i.e; ratio of the post-vaccination GMT and the pre-vaccination GMT) Twenty one days after the second dose, a 4-fold increase in serum neutralising antibody titers was obtained in 77.1% of subjects against the A/Indonesia/5/2005 strain, in 75.0% of subjects against A/Anhui/01/2005 and in 85.0% of subjects against A/Turkey/Turkey/1/2005.

The consistency study confirmed that the candidate vaccine induces a cross-reactive immune response against A/Indonesia/5/2005. Twenty-one days after the second dose, seroconversion and seroprotection rates against this strain variant were both 50.2% with a seroconversion factor of 4.9. A 4-fold increase in serum neutralising antibody titers was obtained in 91.4% of subjects.

The ability of the vaccine to induce cross-reactivity and cross-protection against a variant of the vaccine strain was assessed non-clinically using a ferret challenge model. Four groups of 6 ferrets were immunized intramuscularly with an AS03 adjuvanted vaccine containing 15, 7.5, 3.8 or 1.7 µg of HA derived from H5N1/A/Vietnam/1194/04 (NIBRG-14). The two control groups included ferrets immunized with adjuvant alone or non-adjuvanted vaccine (15 µg HA). Ferrets were vaccinated on days 0 and 21 and challenged intratracheally on day 49 with a lethal dose of heterologous H5N1/A/Indonesia/5/05. Of the animals receiving adjuvanted vaccine, 96% were protected against the lethal challenge. Viral shedding into the upper respiratory tract was also reduced in vaccinated animals relative to controls, suggesting a reduced risk of viral transmission. In the unadjuvanted control group, as well as in the adjuvant control group, all animals died or had to be euthanized as they were moribund, three to four days after the start of challenge.

INDICATIONS

Prophylaxis of influenza in an officially declared pandemic situation. The vaccine may only be marketed, distributed or supplied in accordance with the directives contained in the New Zealand National Health Emergency Plan; New Zealand Influenza Pandemic Action Plan.

CONTRAINDICATIONS

History of an anaphylactic reaction (i.e. life-threatening) to any of the constituents or trace residues of this vaccine. (Also see Precautions section).

PRECAUTIONS

Caution is needed when administering this vaccine to persons with a known hypersensitivity (other than anaphylactic reaction) to the active substance, to any of the excipients and to residues.

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.

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

PANDEMRIX should under no circumstances be administered intravascularly or intradermally.

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

A protective immune response may not be elicited in all vaccinees.

Syncope (fainting) can occur following, or even before, any vaccination as a psychogenic response to the needle injection. It is important that procedures are in place to avoid injury from faints.

Use in Pregnancy (Category B2):

No data have been generated in pregnant women with *PANDEMRIX* and with the AS03 adjuvant contained in the vaccine. Data from vaccinations with intrapandemic trivalent vaccines in pregnant women do not indicate that adverse foetal and maternal outcomes were attributable to the vaccine.

Animal studies do not indicate direct or indirect harmful effects with respect to fertility, pregnancy, embryonal/foetal development, parturition or post-natal development.

Healthcare providers need to assess the benefits and potential risks of administering the vaccine to pregnant women.

Use in Lactation:

No data have been generated in breast-feeding women.

Interactions

No data are available on the concomitant administration of *PANDEMRIX* with other vaccines.

Therefore, *PANDEMRIX* is not intended to 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.

False positive ELISA serologic tests for HIV-1, Hepatitis C, and especially HTLV-1 may occur following influenza vaccination. These transient false-positive results may be due to cross-reactive IgM elicited by the vaccine. For this reason, a definitive diagnosis of HIV-1, Hepatitis C, or HTLV-1 infection requires a positive result from a virus-specific confirmatory test (e.g., Western Blot or immunoblot).

ADVERSE REACTIONS

Clinical Trial Experience

Adverse reactions from clinical trials with the mock-up vaccine are listed here below (see 'Clinical Trials' section for more information on mock-up vaccines).

The incidence of symptoms has been evaluated in more than 5,000 subjects 18 years old and above who received formulations containing at least 3.8 µg HA.

Undesirable effects reported are listed within body systems and categorised by frequency according to the following definitions:

Very common ($\geq 1/10$)

Common ($\geq 1/100$ to $< 1/10$)

Uncommon ($\geq 1/1,000$ to $< 1/100$)

Rare ($\geq 1/10,000$ to $< 1/1,000$)

Very rare ($< 1/10,000$)

Not known (cannot be estimated from the available data).

Blood and lymphatic system disorders: *Common:* lymphadenopathy

Nervous system disorders: *Very common:* headache; *Uncommon:* dizziness, somnolence, paraesthesia

Psychiatric disorders: *Uncommon:* insomnia

Gastrointestinal disorders: *Uncommon:* gastro-intestinal symptoms (such as nausea, diarrhoea, vomiting, abdominal pain)

Skin and subcutaneous tissue disorders: *Common:* ecchymosis at the injection site, increased sweating; *Uncommon:* pruritus, rash

Musculoskeletal and connective tissue disorders: *Very common:* myalgia, arthralgia

General disorders and administration site conditions: *Very common:* pain, redness, swelling and induration at the injection site, fatigue, fever; *Common:* injection site reactions (such as warmth, pruritus), shivering, influenza like illness; *Uncommon:* malaise

Post-marketing data

No post-marketing surveillance data are available following *PANDEMRIX*.

From Post-marketing surveillance with interpandemic trivalent vaccines, the following adverse events have been reported:

Blood and lymphatic system disorders: Transient thrombocytopenia.

Immune system disorders: Allergic reactions, in rare cases leading to shock.

Nervous system disorders: Neuralgia, convulsions. Neurological disorders, such as encephalomyelitis, neuritis and Guillain Barré syndrome.

Vascular disorders: Vasculitis with transient renal involvement.

Skin and subcutaneous tissue disorders: Generalised skin reactions including urticaria

DOSAGE AND ADMINISTRATION

Dosage

Adults from the age of 18 to 60 years will receive two doses of *PANDEMRIX*, the first administered at an elected date, the second at least three weeks after the first dose for maximum efficacy.

Vaccination should be carried out by intramuscular injection.

Populations

Children and Elderly

No data have been generated below 18 years and above 60 years of age. The immunogenicity and reactogenicity profile of *PANDEMRIX* in this population is therefore unknown.

In a pandemic situation, administration of the vaccine in those populations shall follow national recommendations.

Method of Administration

PANDEMRIX H5N1 consists of two containers: one multidose vial containing the antigen (suspension) and a second multidose vial containing the adjuvant (emulsion). The suspension is a colourless light opalescent liquid. The emulsion is a whitish to yellowish (milky) homogeneous liquid.

Prior to administration, the two components should be mixed.

Instructions for mixing and administration of the vaccine:

1. Before mixing the two components, the emulsion (adjuvant) and suspension (antigen) should be allowed to reach room temperature; each vial should be shaken and inspected visually for any foreign particulate matter and/or abnormal physical appearance. In the event of either being observed (including rubber particles from the stopper), discard the vaccine.
2. The vaccine is mixed by withdrawing the contents of the vial containing the adjuvant by means of a syringe and by adding it to the vial containing the antigen.

3. After the addition of the adjuvant to the antigen, the mixture should be well shaken. The mixed vaccine is a whitish to yellowish (milky) homogeneous emulsion. In the event of other variation being observed, discard the vaccine.
4. The volume of *PANDEMRIX H5N1* vial after mixing is at least 5 mL. The vaccine should be administered in accordance with the recommended posology (see Dosage and Administration).
5. The vial should be shaken prior to each administration and inspected visually for any foreign particulate matter and/or abnormal physical appearance. In the event of either being observed (including rubber particles from the stopper), discard the vaccine.
6. Each vaccine dose of 0.5 mL is withdrawn into a syringe for injection and administered intramuscularly.
7. After mixing, use the vaccine within 24 hours. The mixed vaccine can either be stored in a refrigerator (2°C - 8°C) or at room temperature not exceeding 25°C. If the mixed vaccine is stored in a refrigerator, it should be allowed to reach room temperature before each withdrawal.

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

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

OVERDOAGE

Insufficient data are available.

For advice on management of over dosage, please contact the Poisons Information Centre on 131126

STORAGE

PANDEMRIX must be stored in a refrigerator between +2°C and +8°C and be protected from light. DO NOT FREEZE.

The expiry date of the vaccine is indicated on the label and packaging. The shelf life of *PANDEMRIX* is 3 years from the date of manufacture if stored between temperatures of +2°C and +8°C.

After mixing, the vaccine should be used within one working day.

PRESENTATIONS

2.5 ml suspension in a vial (type I glass) for 10 doses with a stopper. Pack size of 50.

2.5 ml emulsion in a vial (type I glass) for 10 doses with a stopper. Pack size of 25 X 2.

MANUFACTURER:

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