Prepandrix™

Prepandemic influenza vaccine (split virion, inactivated, AS03 adjuvanted)

QUALITATIVE AND QUANTITATIVE COMPOSITION

Prepandrix™ is an inactivated influenza vaccine (split virion) of a strain with pandemic potential containing antigen (propagated in embryonated eggs) equivalent to A/Indonesia/05/2005 PR8-IBCDC-RG2 (H5N1) adjuvanted with AS03 composed of squalene (10.69 milligrams), DL-α-tocopherol (11.86 milligrams) and polysorbate 80 (4.86 milligrams).

Each 0.5 ml vaccine dose contains 3.75 µg haemagglutinin of the recommended strain and is adjuvanted with AS03.

Excipients: It contains 5 micrograms thiomersal.

PHARMACEUTICAL FORM

Suspension and emulsion for emulsion for injection.

CLINICAL PARTICULARS

Indications

Active immunisation against H5N1 subtype of Influenza A virus. This indication is based on immunogenicity data from healthy subjects from the age of 18 years onwards following administration of two doses of vaccine prepared from A/Indonesia/05/2005 PR8-IBCDC-RG2 (H5N1). ***Prepandrix™*** should be used in accordance with official recommendations.

Dosage and Administration

Adults from the age of 18 years onwards will receive two doses of ***Prepandrix™***, the first administered at an elected date, the second at least three weeks and up to twelve months after the first dose for maximum efficacy.

The experience in children is limited (see *Adverse Reactions* and *Pharmacodynamic Effects*).

Vaccination should be carried out by intramuscular injection preferably into the deltoid muscle or anterolateral thigh (depending on the muscle mass).

Contraindications

History of an anaphylactic reaction (i.e. life-threatening) to any of the constituents or trace residues (egg and chicken protein, ovalbumin, formaldehyde, gentamicin sulphate and sodium deoxycholate) of this vaccine.

Acute severe febrile illness. Immunisation should be postponed.

Warnings and 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 an anaphylactic event following the administration of the vaccine.

Immunisation shall be postponed in patients with severe febrile illness or acute infection.

Prepandrix™ 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.

Epidemiological studies in several countries have reported an association between another pandemic influenza vaccine (Pandemrix H1N1 manufactured in Dresden, Germany) and narcolepsy with or without cataplexy. These studies have described an absolute risk increase of narcolepsy of approximately 1.4 to 8 additional cases per 100,000 vaccinated children/adolescents and approximately 1 additional case per 100,000 vaccinated adults compared to background rates of 0.12 to 0.79 per 100,000 children/adolescents per year and 0.67 to 1.10 per 100,000 adults per year. Further research is needed to investigate the observed association between Pandemrix and narcolepsy.

Interactions

There are no data on co-administration of ***Prepandrix™*** with other vaccines. Therefore, co-administration is not recommended.

However, if administration of ***Prepandrix™*** with another vaccine is deemed necessary following benefit/risk assessment, immunisation should be carried out on separate limbs. In such case, 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).

Pregnancy and Lactation

No data have been generated in pregnant women with ***Prepandrix™*** and with the AS03 adjuvant contained in the vaccine. Data from vaccinations with interpandemic 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, embryonic/foetal development, parturition or post-natal development (see *Pre-clinical Safety Data*).

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

No data have been generated in breast-feeding women.

Effects on Ability to Drive and Use Machines

No studies on the effects on the ability to drive and use machines have been performed.

Adverse Reactions

Clinical trial data

Adults

Clinical studies have evaluated the incidence of adverse reactions in approximately 5,000 subjects 18 years old and above who received ***Prepandrix™*** containing A/Vietnam/1194/2004 (H5N1) strain with at least 3.75 µg HA.

In a clinical trial where a group of subjects (N=250) received ***Prepandrix™*** containing 3.75 microgram HA/AS03 of A/Indonesia/05/2005 (H5N1) strain, the incidence of adverse reactions was similar overall to the one listed below.

Adverse reactions reported are listed per dose 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

Blood and lymphatic system disorders

Common: lymphadenopathy

Psychiatric disorders

Uncommon: insomnia

Nervous system disorders

Very common: headache

Uncommon: dizziness, somnolence, paraesthesia

Gastrointestinal disorders

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

Skin and subcutaneous tissue disorders

Common: ecchymosis at the injection site, sweating increased

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), influenza like illness, shivering

Uncommon: malaise

Children aged 3-9 years

A clinical study evaluated the reactogenicity in children 3 to 5 and 6 to 9 years of age who received either a full (0.5 ml) or a half (0.25 ml) dose of ***Prepandrix™*** containing A/Vietnam/1194/2004 (H5N1) strain.

The per-dose frequency of the adverse reactions was as follows:

Adverse reactions	3-5 years		6-9 years	
	Half dose	Full dose	Half dose	Full dose
Injection site induration	9.9%	18.6%	12.0%	12.2%
Injection site pain	48.5%	62.9%	68.0%	73.5%
Injection site redness	10.9%	19.6%	13.0%	6.1%
Injection site swelling	11.9%	24.7%	14.0%	20.4%
Injection site ecchymosis	9.9%	4.1%	3.0%	0.0%
Fatigue	NS	NS	8.0%	15.3%
Fever (any)	5.9%	17.5%	7.0%	21.4%
Fever (>39°C)	2.0%	5.2%	0%	7.1%
Sweating	2.0%	4.1%	4.0%	6.1%
Gastrointestinal symptoms (including nausea, vomiting, diarrhoea and/or abdominal pain	NS	NS	9.0%	13.3%
Headache	NS	NS	24.0%	26.5%
Arthralgia	NS	NS	8.0%	9.2%
Myalgia	NS	NS	12.0%	14.3%
Drowsiness	7.9%	13.4%	NS	NS

Irritability	7.9%	18.6%	NS	NS
Loss of appetite	6.9%	16.5%	NS	NS
Shivering	1.0%	12.4%	4.0%	14.3%
Vomiting	3%	3.1%	NS	NS

NS = not solicited

Post-marketing data

No post-marketing surveillance data are available following administration with ***Prepandrix™***.

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.

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

Overdose

Insufficient data are available.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics

Pharmaco-therapeutic group: Influenza vaccines, ATC Code J07BB02

Pharmacodynamic effects

Immune response against A/Indonesia/05/2005 (H5N1)

In a clinical study (Q-Pan-H5N1-001) in which two doss of AS03-adjuvanted vaccine containing 3.75 µg HA derived from A/Indonesia/05/2005 were administered on days 0 and 21 to 140 subjects aged 18-60 years, the anti-HA antibody responses were as follows:

anti-HA antibody	Immune response to A/Indonesia/05/2005		
	Day 21 N=140	Day 42 N=140	Day 180 N=138
Seroprotection rate[1]	45.7%	96.4%	49.3%
Seroconversion rate[2]	45.7%	96.4%	48.6%
Seroconversion factor[3]	4.7	95.3	5.2

[1]seroprotection rate: proportion of subjects with haemagglutination inhibition (HI) titre ≥1:40;
[2]seroconversion rate: proportion of subjects who were either seronegative at pre-vaccination and have a protective post-vacination titre of ≥1:40, or who were seropositive at pre-vaccination and have a 4-fold increase in titre;
[3]seroconversion factor: ratio of the post-vaccination geometric mean titre (GMT) and the pre-vaccination GMT.

A 4-fold increase in serum neutralising antibody titres were observed in 79.2% of subjects twenty-one days after the first dose, 95.8% twenty-one days after the second dose and 87.5% six months after the second dose.

In a second study, 49 subjects aged 18-60 years received two doses of AS03-adjuvanted vaccine containing 3.75µg HA derived from A/Indonesia/05/2005 on days 0 and 21. At days 42, the anti-HA antibody seroconversion rate was 98%, all subjects were seroprotected and the seroconversion factor was 88.6. In addition, all subjects had neutralising antibody titres of at least 1:80.

Administration of an AS03-adjuvanted vaccine containing 3.75 µg HA derived from A/Vietnam/1194/2004 (H5N1)

Paediatric population

In a clinical study (D-Pan-H5N1-009), children aged 3 to 5 and 6 to 9 years old received two doses of either a full (0.5 ml) or a half dose (0.25 ml) of an AS03-adjuvanted vaccine containing 3.75 µg HA derived from A/Vietnam/1194/2004 (H5N1) at 0 and 21 days. At day 42, the anti-HA antibody responses were as follows:

anti-HA antibody	Immune response to A/Vietnam/1194/2004			
	3 to 5 years		6 to 9 years	
	Half dose N=49	Full dose N=44	Half dose N=43	Full dose N=43
Seroprotection rate[1]	95.9%	100%	100%	100%
Seroconversion rate[2]	95.9%	100%	100%	100%
Seroconversion factor[3]	78.5	191.3	108.1	176.7

[1]seroprotection rate: proportion of sbujects with haemagglutination inhibition (HI) titre ≥1:40;
[2]seroconversion rate: propotion 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;
[3]seroconversion factor: ratio of the post-vaccination geometric mean titre (GMT) and the pre-vaccination GMT.

The clinical relevant of the haemagglutincation inhibition (HI) titre ≥1:40 in children is unknown.

Subjects of D-Pan-H5N1-009 were followed up for persistence of the immune response. The seroprotection rates 6, 12 and 24 months after vaccination were as follows:

anti-HA antibody	Immune response to A/Vietnam/1194/2004 3-5 years					
	6 months after vaccination		12 months after vaccination		24 months after vaccination	
	Half dose (N=50)	Full dose (N=29)	Half dose (N=47)	Full dose (N=27)	Half dose (N=27)	Full dose (N=26)
Seroprotection rate[1]	56.0%	82.8%	38.3%	48.1%	38.3%	73.1%

[1]seroprotection rate: proportion of subjects with haemagglutination inhibition (HI) titre ≥1:40

anti-HA antibody	Immune response to A/Vietnam/1194/2004 6-9 years					
	6 months after vaccination		12 months after vaccination		24 months after vaccination	
	Half dose (N=44)	Full dose (N=41)	Half dose (N=37)	Full dose (N=35)	Half dose (N=37)	Full dose (N=34)

Seroprotection rate[1]	63.6%	78.0%	24.3%	62.9%	24.3%	67.6%

[1]seroprotection rate: proportion of subjects ith haemagglutination inhibition (HI) titre ≥1:40

At day 42, and after 6, 12 and 24 months the neutralising antibody responses were as follows:

Serum neutralising antibody	Immune response to A/Vietnam/1194/2004				
	3-5 years				
	21 day after 2nd dose		6 months after vaccination	12 months after vaccination	24 months after vaccination
	Half dose N=47	Full dose N=42	Half dose N=49	Half dose N=47	Half dose N=47
GMT[1]	1044.4	4578.3	781.2	238.9	302.5
Seroconversion rate[2]	95.6%	97.4%	87.2%	82.2%	80.0%
≥1:80[3]	100%	100%	100%	93.6%	95.7%

[1]Geometric Mean Titre
[2]4-fold increase in serum neutralising antibody titre
[3]% of subjects reaching a serum neutralising antibody titre of at least 1:80

Serum neutralising antibody	Immune response to A/Vietnam/1194/2004				
	6-9 years				
	21 day after 2nd dose		6 months after vaccination	12 months after vaccination	24 months after vaccination
	Half dose N=42	Full dose N=42	Half dose N=40	Half dose N=36	Half dose N=38
GMT[1]	1155.1	3032.5	756.1	179.4	234.5
Seroconversion rate[2]	100%	100%	95.0%	67.6%	63.9%
≥1:80[3]	100%	100%	100%	86.1%	97.4%

[1]Geometric Mean Titre
[2]4-fold increase in serum neutralising antibody titre
[3]% of subjects reaching a serum neutralising antibody titre of at least 1:80

Cross-reactive immune response elicited by AS03-adjuvanted vaccine containing 3.75 µg HA derived from A/Indonesia/05/2005 (H5N1)

After two doses of AS03-adjuvanted vaccine containing 3.75 µg HA derived from A/Indonesia/05/2005 administered on days 0 and 21 to 140 subjects aged 18-60 years, the anti-HA antibody responses to A/Vietnam/1194/2004 were as follows:

anti-HA antibody	Immune response to A/Vietnam/1194/2004	
	Day 21 N=140	Day 42 N=140
Seroprotection rate[1]	15%	59.3%
Seroconversion rate[2]	12.1%	56.4%
Seroconversion factor[3]	1.7	6.1

[1]seroprotection rate: proportion of subjects with haemagglutination inhibition (HI) titre ≥1:40;
[2]seroconversion rate: proportion of subjects who were either seronegative at pre-vaccination and have a protective post-vaccination titre ≥1:40, or who were seropositive at pre-vaccination and have a 4-fold increase in titre;
[3]seroconversion factor: ratio of the post-vaccination geometric mean titre (GMT) and the pre-vaccination GMT.

At day 180, the seroprotection rate was 13%.

A 4-fold increase in serum netutralising antibody titres against A/Vietnam was obtained in 49% of subjects twenty-one days after the first dose, 67.3% twenty-one days after the second dose and 44.9% six months after the second dose.

Cross-reactive immune responses elicited by A03-adjuvanted vaccine containing 3.75 µg HA derived from A/Vietnam/1194/2004 (H5N1):

In the subects aged 3 to 5 and 6 to 9 years old who received two doses of either a full or a half dose of AS03-adjuvanted vaccine containing 3.75 µg HA derived from A/Vietnam/1194/2004 (H5N1), the anti-HA antibody responses against A/Indonesia/5/2005 at day 42 were as follows:

anti-HA antibody	Immune response to A/Indonesia/5/2005			
	3 to 5 years		6 to 9 years	
	Half dose N=49	Full dose N=44	Half dose N=43	Full dose N=43
Seroprotection rate[1]	71.4%	95.5%	74.4%	79.1%
Seroconversion rate[2]	71.4%	95.5%	74.4%	79.1%
Seroconversion factor[3]	10.7	33.6	12.2	18.5

[1]seroprotection rate: proportion of subjects with haemagglutination inhibition (HI) titre ≥1:40;
[2]seroconversion rate: proportion of subjects who were either seronegative at pre-vaccination and have a protective post-vaccination titre ≥1:40, or who were seropositive at pre-vaccination and have a 4-fold increase in titre;
[3]seroconversion factor: ratio of the post-vaccination geometric mean titre (GMT) and the pre-vaccination GMT.

Subjects of D-Pan-H5N1-009 were followed up for persistence of the immune response. The seroprotection at month 6, 12 and 24 were as follows:

anti-HA antibody	Immune response to A/Indonesia/5/2005					
	3 to 5 years					
	Month 6		Month 12		Month 24	
	Half dose N=49	Full dose N=27	Half dose N=47	Full dose N=27	Half dose N=47	Full dose N=26
Seroprotection rate[1]	6.1%	70.4%	36.2%	44.4%	10.6%	53.8%

[1]seroprotection rate: proportion of subjects with haemagglutination inhibition (HI) titre ≥1:40

anti-HA antibody	Immune response to A/Indonesia/5/2005					
	6 to 9 years					
	Month 6		Month 12		Month 24	
	Half dose N=42	Full dose N=34	Half dose N=36	Full dose N=35	Half dose N=37	Full dose N=34
Seroprotection rate[1]	4.8%	64.7%	19.4%	42.9%	10.8%	29.4%

[1]seroprotection rate: proportion of subjects with haemagglutination inhibition (HI) titre ≥1:40

Furthermore, in the group of children that received a half dose of vaccine, the rate of subjects with a titre of neutralising antibodies above 1:80 remained high up to 24 months after the first dose. The neutralising antibody responses were as follows:

Serum neutralising antibody	Immune response to A/Indonesia/5/2005							
	3 to 5 years				6 to 9 years			
	Day 42 N=46	Month 6 N=48	Month 12 N=47	Month 24 N=47	Day 42 N=42	Month 6 N=40	Month 12 N=35	Month 24 N=38
GMT[1]	331.4	242.1	177.7	188.5	412.1	208.4	128.1	146.0
Seropositivity rate[2]	95.6%	93.0%	97.9%	97.9%	97.2%	97.3%	94.4%	97.4%
≥1:80[3]	75.6%	72.1%	85.1%	80.9%	88.9%	70.3%	86.1%	81.6%

[1]Geometric Mean Titre
[2]% of subjects with titres ≥1:28
[3]% of subjects reaching a serum neutralising antibody titre of at least 1:80

Alternative schedules

An extended dosing interval was investigated in study D-H5N1-012 in which a group of subjects 18-60 years of age received two doses of Prepandrix containing the A/Vietnam/1194/2004 strain 6 months or 12 months apart. Twenty-one days after the

second dose, the seroprotection rate and the vaccine response rate against A/Vietnam/1194/2004 in subjects who received the vaccine 6 months apart were 89.6% and 95.7% respectively. Twenty-one days after the second dose, the seroprotection rate and the vaccine response rate in subjects who received the vaccine 12 months apart were 92.0% and 100%, respectively.

In this study, cross-reactive immune responses against A/Indonesia/5/2005 were also observed. Twenty-one days after the second dose, the seroprotection rate and the vaccine response rate in subjects who received the vaccine 6 months apart were 83.3% and 100%, respectively. Twenty-one days after the second dose, the seroprotection rate and the vaccine response rate in subjects who received the vaccine 12 months apart were 84.0% and 100%, respectively.

One dose of AS03-adjuvanted vaccine containing 3.75 µg HA derived from A/Indonesia/05/2005 administered after one or two doses of AS03-adjuvanted vaccine containing 3.75 µg HA derived from A/Vietnam/1194/2004.

In a clinical study (D-Pan-H5N1-012), subjects aged 18-60 years received a dose of AS03-adjuvanted vaccine containing 3.75 µg HA derived from either A/Vietnam/1194/2004 or Indonesia/5/2005 six months after they had received one or two priming doses of AS03-adjuvanted vaccine containing 3.75 µg HA derived from A/Vietnam/1194/2004 on day 0 or on days 0 and 21. The anti-HA responses were as follows:

anti-HA antibody	Against A/Vietnam 21 days after boosting with A/Vietnam N=46		Against A/Indonesia 21 days after boosting with A/Indonesia N=49	
	After one priming dose	After two priming doses	After one priming dose	After two priming doses
Seroprotection rate[1]	89.6%	91.3%	98.1%	93.9%
Booster seroconversion rate[2]	87.5%	82.6%	98.1%	91.8%
Booster factor[3]	29.2	11.5	55.3	45.6

[1]seroprotection rate: protection of subjects with haemagglutination inhibition (HI) titre ≥1:40;
[2]booster seroconversion rate: proprotion of subjects who were either seronegative at pre-booster and have a protective post-vaccination titre of ≥1:40, or who were seropositive at pre-booster and have a 4-fold increase in titre;
[3]booster factor: ratio of the post-booster geometric mean titre (GMT) and the pre-booster GMT.

Regardless of whether one or two doses of priming vaccine had been given 6 months earlier, the seroprotection rates against A/Indonesia were >80% after a dose of AS03-adjuvanted vaccine containing 3.75 µg HA derived from A/Vietnam/1194/2004 and

the seroprotection rates against A/Vietnam were >90% after a dose of AS03-adjuvanted vaccine containing 3.75 µg HA derived from A/Indonesia/05/2005. All subjects achieved a neutralising antibody titre of at least 1:80 against each of the two strains regardless of the HA type in the vaccine and the previous number of doses.

In another clinical study (D-Pan-H5N1-015), 39 subjects ageed 18-60 years received a dose of AS03-adjuvanted vaccine containing 3.75 µg HA derived from A/Indonesia/5/2005 fourteen months after they had received two doses of AS03-adjuvanted vaccine containing 3.75 µg HA derived from A/Vietnam/1194/2004 administered on day 0 and day 21. The seroprotection rate against A/Indonesia 21 days after booster vaccination was 92% and 69.2% at day 180.

In another clinical study (D-Pan-H5N1-038), 387 subjects aged 18-60 years received 1 dose of AS03-adjuvanted vaaccine containing 3.75 µg HA derived from A/Indonesia/5/2005 36 months after they had received two doses of A/Vietnam/1194/2004. The seroprotection rate, booster seroconversion rate and booster factor against A/Indonesia/5/2005 21 days after booster vaccination was 100%, 99.7% and 123.8 respectively.

Other information

The anti-HA and neutralising antibody responses to A/Indonesia/05/2005 elicited by AS03-adjuvanted vaccine containing 3.75 µg HA derived from this same strain have been shown to be comparable with the immune responses to A/Vietnam/1194/2004 elicited by AS03-adjuvanted vaccine containing 3.75 µg HA derived from this strain. Therefore, the data that have been generated with AS03-adjuvanted vaccine containing 3.75 µg HA derived from A/Vietnam/1194/2004 are considered to be relevant to the use of AS03-adjuvanted vaccine containing 3.75 µg HA derived from A/Indonesia/05/2005.

In clinical studies that evaluated the immunogenicity of AS03-adjuvanted vaccine containing 3.75 µg HA derived from A/Vietnam/1194/2004 (H5N1) in subjects 18-60 years old, the anti-haemagglutinin (anti-HA) antibody responses were as follows:

anti-HA antibody	Immune response to A/Vietnam/1194/2004				
	0, 21 days schedule (D-Pan-H5N1-002)		0, 6 months schedule (D-Pan-H5N1-012)		
	21 days after 1st dose N=925	21 days after 2nd dose N=924	21 days after 1st dose N=55	7 days after 2nd dose N=47	21 days after 2nd dose N=48
Seroprotection rate[1]	44.5%	94.3%	38.2%	89.4%	89.6%
Seroconversion rate[2]	42.5%	93.7%	38.2%	89.4%	89.6%
Seroconversion factor[3]	4.1	39.8	3.1	38.2	54.2

[1]seroprotection rate: proportion of subjects with haemagglutination inhibition (HI) titre ≥1:40;
[2]seroconversion rate: 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;
[3]seroconversion factor: ratio of the post-vaccination geometric mean titre (GMT) and the pre-vaccination GMT.

After two doses given 21 days or 6 months apart, 96.0% of subjects had a 4-fold increase in serum neutralising antibody titre and 98-100% had a titre of at least 1:80.

Subjects of D-Pan-H5N1-002 were followed up for persistence of the immune response. The seroprotection rates 6, 12, 24 and 36 months after the first dose were as follows:

anti-HA antibody	Immune response to A/Vietnam/1194/2004			
	6 months after the 1st dose N=256	12 months after the 1st dose N=559	24 months after the 1st dose N=411	36 months after the 1st dose N=387
Seroprotection rate[1]	40.2%	23.4%	16.3%	16.3%

[1]seroprotection rate: propotion of subjects with haemagglutination inhibition (HI) titre ≥1:40

In another clinical study (D-Pan-H5N1-010), 297 subjects aged >60 years (stratified in ranges from 61 to 70, 71 to 80 and >80 years of age) received either a single or a double dose of AS03-adjuvanted vaccine containing 3.75µg HA derived from A/Vietnam/1194/2004 (H5N1) at 0 and 21 days. At day 42, the anti-HA responses were as follows:

anti-HA antibody	Immune response to A/Vietnam/1194/2004 (D42)					
	61 to 70 years		71 to 80 years		>80 years	
	Single dose N=91	Double dose N=92	Single dose N=48	Double dose N=43	Single dose N=13	Double dose N=10
Seroprotection rate[1]	84.6%	97.8%	87.5%	93.0%	61.5%	90.0%
Seroconversion rate[2]	74.7%	90.2%	77.1%	93.0%	38.5%	50.0%
Seroconversion factor[3]	11.8	26.5	13.7	22.4	3.8	7.7

[1]serocovnersion rate: proportion of subjects with haemagglutination inhibition (HI) titre ≥1:40;
[2]seroconversion rate: 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;

[3]seroconversion factor: ratio of the post vaccination geometric mean titre (GMT) and the pre-vaccination GMT.

Although an adequate immune response was achieved at day 42 following two administrations of a single dose of AS03-adjuvanted vaccine containing 3.75 µg HA derived from A/Vietnam/1194/2004 (H5N1), a higher response was observed following two administrations of a double dose of vaccine.

Very limited data in seronegative subjects >80 years of age (N=5) showed that no subject achieved seroprotection following two administrations of a single dose of AS03-adjuvanted vaccine containing 3.75 µg HA derived from A/Vietnam/1194/2004 (H5N1). However following two administrations following a double dose of vaccine, the seroprotection rate at day 42 was 75%.

Subjects of D-Pan-H5N1-010 were followed for persistence of the immune response. The seroprotection rates 6, 12 and 24 months after vaccination were as follows:

anti-HA antibody	Immune response to A/Vietnam/1194/2004					
	6 months after vaccination		12 months after vaccination		24 months after vaccination	
	Single dose (N=140)	Double dose (N=131)	Single dose (N=86)	Double dose (N=81)	Single dose (N=86)	Double dose (N=81)
Seroprotection rate[1]	52.9%	69.5%	45.3%	44.4%	37.2%	30.9%

[1]seroprotection rate: proportion of subjects with haemagglutinaton inhibition (HI) titre ≥1:40

In addition, 44.8% and 56.1% of subjects in respective dose groups had a 4-fold increase in serum neutralising antibody titres from day 0 to day 42 and 96.6% and 100% of subjects had a titre of at least 1:80 at day 42.

Twelve and twenty-four months after vaccination, the neutralising antibody titres were as follows:

anti-HA antibody	Immune response to A/Vietnam/1194/2004			
	12 months after vaccination		24 months after vaccination	
	Single dose N=51	Double dose N=54	Single dose N=49	Double dose N=54
GMT[1]	274.8	272.0	391.0	382.8
Seroconversion rate[2]	27.5%	27.8%	36.7%	40.7%
≥1:80[3]	82.4%	90.7%	91.8%	100%

[1]Geometric Mean Time
[2]4-fold increase in serum neutralising antibody titre
[3]% of subjects reaching aserum neutralising antibody titre of at least 1:80

Information from non-clinical studies:

The ability to induce protection against homologous and heterologous vaccine strains was assessed non-clinically using ferret challenge models.

In each experiment, four groups of six ferrets were immunized intramuscularly with an AS03-adjuvanted vaccine containing HA derived from H5N1/A/Vietnam/1194/04 (NIBRG-14). Doses of 15, 5, 1.7 or 0.6 micrograms of HA were tested in the homologous challenge experiement, and doses of 15, 7.5, 3.8 or 1.75 micrograms of HA were tested in the heterologous challenge experiemnt. Control groups included ferrets immunized with adjuvant alone, non-adjuvanted vaccine (15 micrograms HA) or phosphate buffered saline solution. Ferrets were vaccinated on days 0 and 21 and challenged by the intra-tracheal route on day 49 with a lethal dose of either H5N1/A/Vietnam/1194/04 or heterologous H5N1/A/Indonesia/5/05. Of the animals receiving adjuvanted vaccine, 87% and 96% were protected against the lethal homologous or heterologous challenge, respectively. 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 the challenge.

Pharmacokinetics

Evaluation of pharmacokinetic properties is not required for vaccines.

Pre-clinical Safety Data

Animal toxicology and/or pharmacology

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, acute and repeated dose toxicity, local tolerance, fertility, embryo-foetal and postnatal toxicity (up to the end of the lactation period).

PHARMACEUTICAL PARTICULARS

List of Excipients

Polysorbate 80, octoxynol 10, thiomersal, sodium chloride, disodium hydrogen phosphate, potassium dihydrogen phosphate, potassium chloride, magnesium chloride, water for injections.

Incompatibilities

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

Shelf Life

The manufacturing date of the vaccine is indicated on the label and packaging.

After mixing, the vaccine should be used within 24 hours (see also *Instructions for mixing and administration of the vaccine*). Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C.

Special Precautions for Storage

Store at +2°C to +8°C (in a refrigerator).

Do not freeze.

Store in the original packaging in order to protect from light.

Nature and Contents of Container

Prepandrix™ is presented in vials as a multidose presentation.

One pack containing:

- one pack of 50 vials (type I glass) of 2.5 ml suspension (10 x 0.25 ml doses) with a stopper (butyl rubber).
- two packs of 25 vials (type I glass) of 2.5 ml emulsion (10 x 0.25 ml doses) with a stopper (butyl rubber).

The volume after mixing 1 vial of suspension (2.5 ml) with 1 vial of emulsion (2.5 ml) corresponds to 10 doses of vaccine (5 ml).

Instructions for Use/Handling

Prepandrix™ 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 homogeneous milky 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 (allow a minimum of 15 minutes); 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 entire contents of the vial containing the adjuvant by means of a 5 ml syringe and by adding it to the vial containing the antigen. The use of a 23-G needle is recommended. However, in the case this needle size would not be available, the use of a 21-G needle is recommended. The vial containing the adjuvant should be maintained in upside down position to facilitate the withdrawal of the full content.

3. After the addition of the adjuvant to the antigen, the mixture should be well shaken. The mixed vaccine is a whitish to yellowish homogeneous milky liquid emulsion. In the event of other variation being observed, discard the vaccine.

4. Label on the carton the DATE and TIME it was reconstituted for record as the mixed vaccine can be used only within 24 hours.

5. The volume of ***Prepandrix™*** after mixing is at least 5 ml. The vaccine should be administered in accordance with the recommended posology (see section *Dosage and Administration*).

6. 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.

7. Each vaccine dose of 0.5 ml is withdrawn into a 1 ml syringe for injection and administered intramuscularly. The use of a needle gauge not larger than 23-G is recommended.

8. After mixing, use the vaccine within 24 hours. The mixed vaccine can either be stored in a refrigerator (2 ^{o}C to 8^{o}C) or at room temperature not exceeding 25 ^{o}C. If the mixed vaccine is stored in a refrigerator, it should be allowed to reach room temperature (allow a minimum of 15 minutes) before each withdrawal.

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

Not all presentations are available in every country.

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Prepandrix is a trademark of the GlaxoSmithKline group of companies.

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[GlaxoSmithKline logo]