PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

FOCLIVIA®

Pandemic influenza vaccine

(surface antigen, inactivated, adjuvanted with MF59C.1)

Sterile Suspension for Intramuscular Injection

Active Immunizing Agent for the Prevention of Influenza

ATC Code: J07BB02

A/Vietnam/1194/2004 (H5N1) 7.5 micrograms HA per 0.5 mL

Sponsor:

Seqirus UK Limited

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Maidenhead, Berkshire, UK

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Distributed by:

Seqirus Canada Inc.

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Date of Initial Authorization:
January 7, 2021

Date of Revision
March 28, 2023

Submission Control Number: 269813

RECENT MAJOR LABEL CHANGES

Not Applicable

TABLE OF CONTENTS

Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

FOCLIVIA® (inactivated adjuvanted vaccine) is indicated for prophylaxis of influenza in an officially declared pandemic situation in individuals 6 months of age and older.

FOCLIVIA® should be used in accordance with official guidance.

1.1 Pediatrics

Pediatrics (6 months to < 18 years): Based on the data submitted and reviewed by Health Canada, the safety and immunogenicity of FOCLIVIA® in pediatric subjects has been established; therefore, Health Canada has authorized an indication for use in the pediatric populations 6 months of age and older (see 8.2.1 ADVERSE REACTIONS, Clinical Trial Adverse Reactions (Pediatrics); and 14 CLINICAL TRIALS).

Pediatrics (<6 months of age): No data are available in children less than 6 months of age.

2 CONTRAINDICATIONS

FOCLIVIA® is contraindicated in individuals with known severe allergic reactions (e.g., anaphylaxis) to this vaccine, or any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

However, in a pandemic situation where the vaccine is indicated, it may be appropriate to administer this vaccine to individuals with a history of anaphylaxis (as defined above), provided that facilities for resuscitation are immediately available in case of need.

4 DOSAGE AND ADMINISTRATION

4.2 Recommended Dose and Dosage Adjustment

Individuals 6 months of age and older: Two 0.5 mL doses administered with an interval of at least 21 days between doses.

4.4 Administration

The vaccine should be administered by intramuscular injection in the deltoid muscle of the upper arm for persons aged 1 year and older. The injection may be administered in the anterolateral aspect of the thigh in infants aged 6 months through 11 months.

Gently shake before use. After shaking, the normal appearance of the vaccine is a milky-white suspension. Visually inspect the contents of each pre-filled syringe or multi-dose vial for particulate matter and/or variation in appearance prior to administration. If either condition is observed, do not administer the vaccine.

Pre-filled syringe

If you are using a pre-filled syringe fitted with a LUER-LOK® attachment, remove the tip cap by unscrewing it in a counter-clockwise direction. Once the tip cap is removed, attach a needle to the

syringe by screwing it on in a clockwise direction until it locks. Once the needle is locked in place, remove the needle protector and administer the vaccine.

Multi-dose vial

Use a separate sterile needle and syringe for each dose withdrawn from the multi-dose vial. It is recommended that small syringes (0.5 mL or 1 mL) be used to minimize any product loss. The multi-dose vial must be used within 28 days from removal of the first dose, and between uses, should be returned to the recommended storage conditions between 2°C and 8°C.

FOCLIVIA® must not be mixed with other products in the same syringe or vial.

Please refer to the Canadian Immunization Guide, Public Health Agency of Canada, for general information regarding vaccine administration practices.

4.5 Missed Dose

The vaccination series consists of two doses administered at least 3 weeks apart. In case the second dose is missed, it should be administered as soon as possible.

5 OVERDOSAGE

There is no experience of overdose with FOCLIVIA®.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

To help ensure the traceability of vaccines for patient immunization record-keeping as well as safety monitoring, health professionals should record the time and date of administration, quantity of administered dose (if applicable), anatomical site and route of administration, brand name and generic name of the vaccine, the product lot number and expiry date.

Table 1: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intramuscular Injection	Pre-filled syringe/ Multi-dose vials Each 0.5 mL contains 7.5 mcg haemagglutinin (HA) of A/Vietnam/1194/2004 (H5N1) *Note: The virus strain will be updated based on the pandemic virus strain recommended by the World Health Organization (WHO) at the time of the*	Excipients: Calcium chloride dihydrate, disodium phosphate dihydrate, magnesium chloride hexahydrate, potassium chloride, potassium dihydrogen phosphate, sodium chloride, thimerosal* and water for injections. Adjuvant: MF59C.1 (MF59®) Citric acid, polysorbate 80, sodium citrate, sorbitan trioleate, squalene and water for injections. Manufacturing Process Residuals: Each dose may also contain the following trace

	declaration of a pandemic.	residues from the manufacturing process: cetyltrimethylammonium bromide (CTAB), egg proteins (including ovalbumin), formaldehyde, hydrocortisone, kanamycin sulphate and neomycin sulphate.

*Multi-dose vials only

Packaging

FOCLIVIA® sterile suspension for injection is supplied in three presentations:

- 0.5 mL suspension in needle-free pre-filled syringes (type I glass), with a plunger-stopper (bromo-butyl rubber) and fitted with a LUER-LOK® attachment (needles not supplied).
- 0.5 mL suspension in pre-filled syringes (type I glass), with a plunger-stopper (bromo-butyl rubber) with a staked needle.
- 5 mL in multi-dose vial (type I glass) with stopper (halo-butyl rubber).

FOCLIVIA® 0.5 mL pre-filled syringes contain no preservatives.

FOCLIVIA® 5 mL multi-dose vial formulation contains thimerosal, a mercury derivative, added as a preservative. Each 0.5 mL dose from the multi-dose vial contains 50 mcg thimerosal.

The tip caps and plungers of the pre-filled syringes and the multi-dose vial stopper are not made with natural rubber latex.

All presentations of FOCLIVIA® are considered safe for use in persons with latex allergies.

7 WARNINGS AND PRECAUTIONS

General

A protective response may not be elicited in all vaccine recipients.

Since a second dose is recommended, it should be noted that there are no safety, immunogenicity or efficacy data to support interchangeability of FOCLIVIA® with other H5N1 monovalent vaccines.

Caution is needed when administrating this vaccine to persons with a known hypersensitivity to the active substance, to any of the excipients or to residues listed in SECTION 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

As with all injectable vaccines, appropriate medical treatment, including epinephrine, and supervision should always be readily available to manage possible anaphylactic reactions following the administration of the vaccine.

If the pandemic situation allows, immunization should be postponed in patients with febrile illness until the fever resolves.

Syncope (fainting) can occur following, or even before, any vaccination as a psychogenic response to the needle injection. Procedures should be in place to prevent injury from fainting and manage syncopal reactions.

Hematologic

As with other intramuscular injections, FOCLIVIA® should be given with caution in individuals with bleeding disorders, such as hemophilia, or individuals currently on anticoagulant therapy, to avoid the

risk of hematoma following the injection.

Immune

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

Neurologic

If Guillain-Barré syndrome (GBS) has occurred within 6 weeks of receipt of prior influenza vaccine, the decision to give FOCLIVIA® should be based on careful consideration of the potential benefits and risks.

7.1 Special Populations

7.1.1 Pregnant Women

The safety of FOCLIVIA® in pregnancy has not been assessed in clinical trials. Limited data obtained from women who became pregnant during the course of clinical trials with FOCLIVIA® (H5N1) or other pandemic vaccines adjuvanted with MF59® were insufficient to inform vaccine-associated risks in pregnancy.

Based on reproductive toxicology data in rabbits, FOCLIVIA® is not predicted to increase the risk of developmental abnormalities.

Another pandemic influenza vaccine, Focetria® (H1N1), containing the same adjuvant (MF59®) and manufactured with the same platform as FOCLIVIA®, was administered outside Canada during the 2009 influenza pandemic, and it is estimated that more than 90,000 women were vaccinated during pregnancy. Post-marketing spontaneously reported adverse events and an interventional study do not suggest direct or indirect harmful effects of Focetria® exposure on pregnancy.

In addition, two large observational studies designed to assess the safety of Focetria® exposure in pregnancy showed no increase in the rates of gestational diabetes, preeclampsia, abortions, stillbirth, low birth weight, prematurity, neonatal deaths, or congenital malformations among almost 10,000 vaccinated pregnant women and their offspring compared with unvaccinated controls.

Healthcare providers should assess the benefit and potential risks of administering the vaccine to pregnant women taking into consideration any official recommendations.

7.1.2 Breast-feeding

FOCLIVIA® has not been evaluated in nursing mothers.

7.1.3 Pediatrics

Pediatrics (< 6 months): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for use in children less than 6 months of age.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The safety of FOCLIVIA® has been assessed in 13 studies, in which 4928 adults 18-60 years, 970 elderly subjects > 60 years and 334 pediatric subjects 6 months to < 18 years received at least one vaccination with either the 7.5 mcg or the 15 mcg MF59® adjuvanted H5N1 (aH5N1) formulation containing either

A/Vietnam/1194/2004 or A/turkey/Turkey/1/2005.

Overall, across all age groups, most solicited local and systemic adverse reactions after administration of FOCLIVIA® were of short duration, with onset close to the time of vaccination, and were mild or moderate in severity.

Adverse event information is derived from clinical trials with FOCLIVIA®. The most commonly reported adverse reactions in adults and children from two key studies, V87P13 and V87P6, respectively, are described below.

In adults 18-60 years, the most commonly reported (≥10%) local adverse reactions were injection site pain, erythema, induration and swelling. The most commonly reported (≥10%) systemic adverse reactions after any vaccination were myalgia, headache and fatigue.

In elderly > 60 years, the most commonly reported (≥10%) local adverse reactions were injection site pain and erythema. The most commonly reported (≥10%) systemic adverse reactions after any vaccination were myalgia and headache. The rates of solicited adverse reactions were, generally, lower in the elderly population > 60 years of age compared to younger adults.

In the pediatric population 6 - 36 months, the most commonly reported (≥10%) local adverse drug reactions were injection site erythema, tenderness, induration, swelling and ecchymosis. The most commonly reported (≥10%) systemic adverse reactions were unusual crying, irritability, sleepiness, diarrhea and change in eating habits.

In children 3 - 18 years, the most commonly (≥10%) reported local adverse reactions were injection site pain, induration, swelling and ecchymosis. The most commonly reported (≥10%) systemic adverse reactions were headache, myalgia, fatigue, malaise, nausea, sweating and chills.

8.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Adult population 18 years of age and older

Study V87P13 was a phase 3, randomized, controlled, observer-blind, multicentre clinical study to assess the safety, tolerability and immunogenicity of two doses of FOCLIVIA® or the MF59-adjuvanted seasonal trivalent influenza vaccine comparator (FLUAD®; aTIV) administered 3 weeks apart. A total of 3647 subjects (3372 adults 18 – 60 years, and 275 elderly > 60 years) were enrolled in the study. Solicited local and systemic reactions were collected for 7 days after vaccination. Unsolicited adverse events were collected for 21 days after last vaccination and serious adverse events (SAEs) for 1 year after last vaccination.

The incidence of solicited local and systemic adverse reactions reported within 7 days of vaccination in study V87P13 is presented in Table 2.

Table 2: Incidence of Solicited Local and Systemic Adverse Reactions[1] in Adult and Elderly Subjects Reported Within 7 Days of Vaccination (Study V87P13)

	Percentage of Subjects Reporting Solicited Reactions[2]							
	Adults 18 - 60 years				Elderly > 60 years			
	FOCLIVIA®		aTIV		FOCLIVIA®		aTIV	
Vaccination	1st (N=2606)	2nd (N=2556)	1st (N=656)	2nd (N=638)	1st (N=214)	2nd (N=212)	1st (N=54)	2nd (N=53)
Local Reactions								
Pain	51% (1%)	38% (<1%)	61% (2%)	45% (0)	30% (0)	22% (<1%)	24% (0)	30% (0)
Erythema	17% (<1%)	17% (<1%)	23% (1%)	20% (1%)	15% (0)	10% (0)	19% (0)	13% (2%)
Induration	14% (<1%)	13% (<1%)	21% (2%)	16% (1%)	9% (<1%)	2% (0)	7% (0)	15% (2%)
Swelling	11% (<1%)	9% (<1%)	18% (1%)	15% (2%)	7% (<1%)	3% (0)	9% (0)	2% (0)
Ecchymosis	6% (0)	4% (<1%)	8% (0)	6% (<1%)	6% (0)	5% (0)	4% (0)	11% (0)
Systemic Reactions								
Myalgia	26% (<1%)	19% (<1%)	37% (2%)	21% (0)	20% (0%)	13% (<1%)	17% (0)	19% (0)
Headache	18% (1%)	14% (1%)	23% (2%)	12% (<1%)	12% (1%)	10% (0)	13% (0)	6% (0)
Fatigue	17% (1%)	14% (1%)	24% (2%)	13% (1%)	8% (<1%)	8% (<1%)	9% (0)	8% (2%)
Malaise	9% (1%)	6% (1%)	17% (1%)	7% (<1%)	7% (0)	6% (<1%)	6% (0)	6% (2%)
Chills	8% (<1%)	7% (<1%)	14% (1%)	8% (<1%)	9% (0)	8% (<1%)	11% (0)	9% (0)
Sweating	6% (<1%)	4% (<1%)	8% (1%)	3% (<1%)	3% (0)	2% (0)	2% (0)	2% (0)
Nausea	5% (<1%)	3% (<1%)	8% (<1%)	4% (<1%)	4% (0)	3% (0)	4% (0)	2% (2%)
Arthralgia	4% (<1%)	4% (<1%)	9% (<1%)	5% (0)	3% (0)	5% (<1%)	4% (0)	6% (0)
Fever ≥ 38.0°C	1% (0)	<1% (0)	2% (<1%)	<1% (0)	0	<1% (0)	0	2% (0)

aTIV = MF59-adjuvanted trivalent influenza vaccine (FLUAD®)
[1] All solicited local and systemic adverse events reported within 7 days of vaccination are included.
[2] Percentage of severe adverse reactions are presented in parenthesis.
Definition of severe reactions: Erythema, Induration Swelling, and Ecchymosis: Any= ≥1 mm, Severe= >50 mm; Pain and systemic adverse reactions: Severe = unable to perform daily activity; Fever: Severe = ≥ 40.0 °C

Within 21 days of vaccination with FOCLIVIA®, the following unsolicited adverse events were reported as possibly/probably related at a rate ≥1% in adults 18 - 60 years of age: fatigue (1%), injection site hemorrhage (1%), nasopharyngitis (1%), upper respiratory tract infection (1%), oropharyngeal pain (1%), rhinitis (1%) and headache (1%).

Within 21 days of vaccination with FOCLIVIA®, the following unsolicited adverse events were reported as possibly/probably related at a rate ≥1% in adults > 60 years of age and older: injection site hemorrhage (1%), upper respiratory tract infection (1%), oropharyngeal pain (1%) and ecchymosis (1%).

One SAE, anaphylaxis, was considered related. No adverse events leading to death were reported as related to FOCLIVIA®.

Special populations

Adverse reactions in special populations have been evaluated in two clinical studies, V87_25 and V87_26, involving 409 adult (18 - 60 years) and 417 elderly (> 60 years) subjects who were either healthy or with underlying medical conditions or immunosuppressive conditions.

Across studies V87_25 and V87_26, the safety of aH5N1 (A/turkey/Turkey/1/2005) in healthy adult and elderly subjects was consistent with safety data from clinical trials with FOCLIVIA®. However, in immunocompromised subjects 18 - 60 years of age, slightly higher rates of nausea (13.0%) were reported. In addition, higher rates of arthralgia (up to 23.3%) were reported in both adult and elderly subjects, who were immunocompromised or with underlying medical conditions.

The following solicited adverse reactions were additionally collected in these two studies and reported with the following frequencies across subjects who received aH5N1 (A/turkey/Turkey/1/2005) irrespective of age or health status: diarrhea (up to 11.9%), loss of appetite (up to 10.9%) and vomiting (up to 1.7%). In both studies, subjects with underlying medical and immunosuppressive conditions reported higher frequencies of diarrhea, loss of appetite and vomiting compared to healthy subjects (irrespective of age)

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

Pediatric population 6 months to less than 18 years of age

The safety of FOCLIVIA® in the pediatric population was assessed in Study V87P6. This was a randomized, controlled, observer-blind, study in which 471 children 6 months to less than 18 years of age were enrolled to receive FOCLIVIA® or the MF59-adjuvanted seasonal influenza vaccine, FLUAD® (aTIV).

In this study, a primary series of two doses of either FOCLIVIA® or FLUAD® were administered 3 weeks apart. A booster dose of FOCLIVIA® was administered 12 months after the second dose.

Solicited local and systemic adverse reactions were collected for 7 days after vaccination. Unsolicited AEs were collected for 21 days after each vaccination and SAEs were collected for 1 year after last vaccination.

The incidence of solicited local and systemic adverse reactions reported within 7 days of vaccination in study V87P6 is presented in Table 3.

Table 3: Incidence of Solicited Local and Systemic Adverse Reactions[1] Reported in the Pediatric Population 6 months to less than 18 years of age within 7 days of Vaccination (Study V87P6)

Percentage of Subjects Reporting Solicited Reactions[2]					
Local Reactions					
	Injection 1		**Injection 2**		**Injection 3***
Age Groups	**FOCLIVIA®**	**aTIV**	**FOCLIVIA®**	**aTIV**	**FOCLIVIA®**
Toddlers 6 to < 36 months	**N=145**	**N=56**	**N=138**	**N=56**	**N=124**
Erythema	32% (1%)	32% (1%)	33% (1%)	27% (0%)	44% (12%)
Tenderness	26% (0%)	29% (0%)	24% (0%)	21% (0%)	46% (0%)
Induration	11% (0%)	5% (0%)	10% (0%)	2% (0%)	32% (6%)
Swelling	12% (1%)	4% (0%)	7% (1%)	4% (0%)	27% (8%)
Ecchymosis	10% (0%)	9% (0%)	5% (0%)	5% (0%)	10% (1%)
Children 3 to < 9 years	**N=96**	**N=40**	**N=93**	**N=39**	**N=85**
Pain	51% (1%)	48% (5%)	53% (0%)	36% (5%)	68% (0%)

Erythema	1% (1%)	30% (3%)	25% (1%)	36% (3%)	41% (0%)
Induration	11% (1%)	10% (3%)	6% (0%)	13% (3%)	18% (0%)
Swelling	9% (1%)	10% (3%)	9% (1%)	13% (3%)	19% (0%)
Ecchymosis	5% (0%)	10% (0%)	8% (0%)	5% (0%)	4% (0%)
Adolescents 9 to < 18 years	**N=93**	**N=41**	**N=91**	**N=40**	**N=83**
Pain	78% (3%)	71% (5%)	65% (2%)	63% (0%)	80% (2%)
Erythema	16% (1%)	20% (0%)	23% (0%)	23% (0%)	28% (1%)
Induration	10% (0%)	7% (2%)	18% (1%)	3% (0%)	25% (1%)
Swelling	11% (1%)	17% (2%)	13% (2%)	18% (0%)	25% (1%)
Ecchymosis	4% (0%)	10% (0%)	5% (0%)	0% (0%)	7% (0%)
Systemic Reactions					
	FOCLIVIA®	**aTIV**	**FOCLIVIA®**	**aTIV**	**FOCLIVIA®**
Toddlers 6 to < 36 months	**N=145**	**N=56**	**N=138**	**N=56**	**N=124**
Unusual Crying	33%	30%	27%	16%	23%
Irritability	39%	21%	29%	20%	27%
Sleepiness	23%	20%	21%	14%	20%
Diarrhea	19%	14%	15%	16%	11%
Change in Eating habits	19%	16%	16%	14%	19%
Vomiting	8%	5%	2%	4%	2%
Unusual Sweating	6%	0%	1%	2%	4%
Shivering	1%	7%	1%	4%	6%
Fever ≥ 38°C (≥ 40°C)	4% (0%)	5% (0%)	2% (0%)	5% (0%)	6% (1%)
Children 3 to < 9 years	**N=96**	**N=40**	**N=93**	**N=39**	**N=85**
Headache	17% (0%)	23% (0%)	9% (1%)	23% (0%)	16% (2%)
Fatigue	15% (0%)	33% (3%)	16% (0%)	21% (0%)	25% (2%)
Myalgia	6% (0%)	13% (3%)	8% (0%)	21% (3%)	25% (2%)
Malaise	6% (0%)	10% (3%)	12% (1%)	15% (0%)	13% (0%)
Chills	6% (0%)	10% (3%)	5% (0%)	15% (0%)	9% (0%)
Diarrhea	10% (1%)	5% (0%)	9% (2%)	5% (0%)	7% (0%)
Nausea	6% (0%)	5% (3%)	10% (0%)	8% (5%)	4% (0%)
Sweating	5 %(0%)	8% (0%)	3% (1%)	10% (0%)	4% (0%)
Fever ≥ 38°C	4% (0%)	5% (0%)	2% (0%)	5% (0%)	6% (1%)
Vomiting	2% (1%)	8% (3%)	4% (0%)	3% (3%)	1% (0%)
Arthralgia	2% (0%)	5% (0%)	1% (0%)	0% (0%)	4%(0%)
Adolescents 9 to < 18 years	**N=93**	**N=41**	**N=91**	**N=40**	**N=83**
Headache	40% (1%)	59% (2%)	22% (0%)	25% (3%)	35% (6%)
Myalgia	37% (2%)	37% (0%)	33% (1%)	18% (0%)	42% (2%)
Fatigue	32% (0%)	49% (0%)	11% (1%)	25% (0%)	20% (2%)

Malaise	22% (0%)	37% (2%)	14% (0%)	13% (0%)	14% (2%)
Nausea	14% (0%)	24% (2%)	9% (1%)	15% (3%)	8% (0%)
Sweating	13% (0%)	15% (0%)	4%(0%)	5% (0%)	5% (0%)
Chills	11% (0%)	34% (0%)	3% (0%)	5% (0%)	14% (2%)
Arthralgia	4% (0%)	10% (0%)	2% (0%)	5% (0%)	4% (0%)
Diarrhea	4% (0%)	10% (0%)	8% (1%)	3% (0%)	8% (0%)
Vomiting	1% (0%)	5% (0%)	1% (0%)	0% (0%)	0% (0%)
Fever ≥ 38°C	0% (0%)	2% (0%)	1% (0%)	0% (0%)	2% (0%)

aTIV = MF59-adjuvanted trivalent influenza vaccine (FLUAD®)
[1] All solicited local and systemic adverse events reported within 7 days of vaccination are included.
[2] Percentage of severe adverse reactions are presented in parenthesis.
Definition of severe reactions: Erythema, Induration, Swelling and Ecchymosis: Any = ≥1 mm, Severe= >50 mm
Malaise, Myalgia, Arthralgia, Headache, Sweating, Nausea, Vomiting, Diarrhea, Fatigue, Fever: Severe = (≥ 40 °C)
*No comparator for 3rd (booster) injection.

Within 21 days of vaccination with FOCLIVIA®, the following unsolicited events were reported as possibly or probably related above 2% across any age group and vaccination: rhinitis (3%), cough (2%), crying (2%), diarrhea (2%), irritability (2%), nasopharyngitis (2%), injections site hemorrhage (2%), ecchymosis (2%) and upper respiratory tract infection (2%). No SAEs were considered related to vaccination. No deaths were reported in the study.

8.3 Less Common Clinical Trial Adverse Reactions

See 8 ADVERSE REACTIONS, Clinical Trial Adverse Reactions.

8.3.1 Less Common Clinical Trial Adverse Reactions – Pediatrics

See 8 ADVERSE REACTIONS, Clinical Trial Adverse Reactions.

8.5 Post-Market Adverse Reactions

No post-marketing surveillance data are available following administration of FOCLIVIA® pandemic vaccine.

Another pandemic influenza vaccine, Focetria® (H1N1), containing the same adjuvant (MF59®) and manufactured with the same process as FOCLIVIA®, was administered outside Canada during the 2009 influenza pandemic. The following adverse events were identified:

Blood and lymphatic system disorders

Lymphadenopathy.

Immune system disorders

Allergic reactions, anaphylaxis including dyspnoea, bronchospasm, laryngeal oedema, in rare cases leading to shock.

Nervous system disorders

Headache, dizziness, somnolence, neurological disorders, such as neuralgia, paraesthesia, convulsions and neuritis.

Cardiac disorders

Palpitation, tachycardia.

Gastrointestinal disorders

Gastrointestinal disorders such as nausea, vomiting, abdominal pain and diarrhea.

Skin and subcutaneous tissue disorders

Generalized skin reactions including pruritus, urticaria or non-specific rash; angioedema.

Musculoskeletal, connective tissue and bone disorders

Muscular weakness, pain in extremities.

General disorders and administration site conditions

Asthenia.

Respiratory disorders

Cough.

The following additional adverse events were reported from post-marketing surveillance with seasonal non-adjuvanted trivalent vaccines in all age groups and a seasonal trivalent MF59-adjuvanted subunit influenza vaccine approved for use in elderly subjects 65 years of age and older:

Blood and lymphatic system disorders

Thrombocytopenia (in some cases reversible platelet counts less than 5000 mm3).

Nervous system disorders

Neurological disorders, such as encephalomyelitis and Guillain Barré syndrome.

Vascular disorders

Vasculitis which may be associated with transient renal involvement.

Skin and subcutaneous tissue disorders

Erythema multiforme.

General disorders and administration site conditions

Extensive swelling of injected limb lasting more than one week, injection-site cellulitis-like reaction (some cases of swelling, pain, and redness extending more than 10 cm and lasting more than 1 week).

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

There are no data on co-administration of FOCLIVIA® with vaccines other than non-adjuvanted seasonal influenza vaccines. If co-administration with another vaccine is considered, immunization should be carried out on separate limbs. It should be noted that adverse reactions may be intensified.

9.4 Drug-Drug Interactions

Concomitant use with other vaccines

Data obtained in adults showed that co-administration of FOCLIVIA® and seasonal (inactivated surface antigen, non-adjuvanted) influenza vaccine did not lead to any interference in the form of altered

immune responses. Co-administration was also not associated with higher rates of local or systemic reactions compared to administration of FOCLIVIA® alone.

Therefore, the data indicate that FOCLIVIA® may be co-administered with non-adjuvanted seasonal influenza vaccines (with injections made into separate limbs).

Concurrent use with immunosuppressive therapies

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

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

An influenza pandemic occurs when humans generally have little or no immunity to a new influenza virus strain and this virus strain is rapidly transmitted from human to human. Antigenic variants of H5N1 viruses as an example, have been in circulation in the avian species globally, with rare transmission to humans. However, these avian H5N1 viruses may acquire mutations that facilitate transmission among humans. Antibody against one influenza type or subtype may confer little or no protection against another virus. Furthermore, antibody to one antigenic variant of influenza virus might not protect against a new antigenic variant of the same type or subtype.

A specific post-vaccination hemagglutination-inhibition (HI) antibody titer has not been correlated with protection from H5N1 influenza illness; however, HI titers have been used as a measure of influenza vaccine activity. In some human challenge studies with other influenza virus strains, antibody titers of ≥1:40 have been associated with protection from influenza illness in up to 50% of subjects.

FOCLIVIA® contains the adjuvant MF59C.1, which is designed to induce a greater antigen-specific immune response when compared to non-adjuvanted influenza vaccines, while broadening and extending the duration of the immune response.

10.2 Pharmacodynamics

See 14.4 IMMUNOGENICITY.

10.3 Pharmacokinetics

Not applicable.

11 STORAGE, STABILITY AND DISPOSAL

Store under refrigeration at 2° to 8°C. Do not freeze. Discard if the vaccine has been frozen. Protect from exposure to light. Do not use after the expiration date.

Between uses, return the multi-dose vial to the recommended storage conditions.

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

12 SPECIAL HANDLING INSTRUCTIONS

Gently shake before use.

After shaking, the normal appearance of the vaccine is a milky-white suspension.

Visually inspect the contents of each pre-filled syringe or multi-dose vial for particulate matter and/or variation in appearance prior to administration. If either condition is observed, do not administer the vaccine.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

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

A/Vietnam/1194/2004 (H5N1)	7.5 micrograms HA**

per 0.5 mL dose

* propagated fertilized hens' eggs from healthy chicken flocks

** haemagglutinin

Proper name: Pandemic Influenza Vaccine (surface antigen, inactivated, grown in embryonated chicken eggs)

Pharmaceutical standard: this vaccine complies with the WHO recommendations for the pandemic.

Product Characteristics:

FOCLIVIA® is a sterile milky-white suspension.

The influenza virus strain is grown in embryonated chicken eggs and inactivated by formaldehyde treatment before purification of the surface antigens and formulation with the MF59C.1 adjuvant.

The vaccine is presented as a suspension for injection in pre-filled syringe or multi-dose vial. The multi-dose vial also contains thimerosal as a preservative.

The MF59C.1 adjuvant is an oil-in-water emulsion, composed mainly of squalene that is an intermediate metabolite in the synthesis of cholesterol.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

An overview of 4 key studies in healthy individuals 6 months of age or older is given in Table 4 below. Two doses of A/Vietnam/1194/2004 were administered with an interval of 3 weeks in these studies.

In addition, information from 6 supportive trials is referenced throughout Section 14. In 3 of the supportive studies (V87P2, V87P3, and V87P12) subjects received two doses of A/Vietnam/1194/2004. In supportive trials V87P11, V87_25 and V87_26 subjects received two doses of A/turkey/Turkey/1/2005.

Table 4: Summary of Study Design and Subject Demographics for Key Clinical Trials in individuals 6 Months of Age and Older for Prophylaxis of Influenza in an Officially Declared Pandemic

Study #	Study design	Dosage, route of administration and duration	Study subjects (N)*	Mean age (Range)**	Sex**
V87P1	**Phase 2** Randomized (1:1), Controlled, Observer-blind, Multi-center	A/Vietnam/H5N1: 7.5 mcg, 15 mcg Two 0.5 mL IM injections, 3 weeks apart, with a 0.5 mL IM booster on Day 202	313 (18 - 60 years): 157, 156 173 (> 60 years): 87, 86 Total: 486 (Healthy)	18 - 60 years: 42.8 years (18 - 60) > 60 years: 70.5 years (61- 90)	18 - 60 years: M = 45% F = 55% > 60 years: M = 58% F = 42%
V87P13	**Phase 3** Randomized (4:1), Controlled, Observer-blind, Multi-center	TIV + A/Vietnam/H5N1: 7.5 mcg -Placebo + aTIV Two 0.5 mL IM injections 3 weeks apart***	2692[2] (18 - 60 years) 219 (> 60 years) 679 (18 - 60 years) 56 (> 60 years) Total: 3646[2] (Healthy)	18 - 60 years: 40.7 years (18 - 60) > 60 years: 61.9 years (61 - 68)	18 - 60 years: M = 44% F = 56% > 60 years: M = 50% F = 50%
V87_17	**Phase 2** Randomized (1:1), Controlled, Double-blind, Multi-center	A/Vietnam/H5N1: 3.75 mcg, 7.5 mcg Two 0.5 mL IM injections 3 weeks apart	385 (18 – 60 years) 191, 194 337 (> 60 years) 166, 171 Total 722 (Healthy)	3.75 mcg: 35.1 years (18 - 60) 68.2 years (61 - 82) 7.5 mcg: 36.9 years (18 - 60) 68.7 years (61 - 89)	18 - 60 years: 3.75 mcg: M = 52% F = 48% 7.5 mcg M = 57% F = 43% > 60 years: 3.75 mcg: M = 47% F = 53% 7.5 mcg: M = 50% F = 50%

Study #	Study design	Dosage, route of administration and duration	Study subjects (N)*	Mean age (Range)**	Sex**
V87P6	**Phase 2** Randomized (3:1), Controlled, Observer-blind, Single-center	A/Vietnam/H5N1: 7.5 mcg TIV: 7.5 mcg Two 0.5 mL IM injections, 3 weeks apart, with a 0.5 mL IM booster on Day 382	335 (6 months - 18 years) 137 (6 months - 18 years) Total: 472 (Healthy)	6 months – 36 months: 19.1 years (6 - 34) 3 years – < 9 years: 5.5 years (3 - 8) 9 years – < 18 years: 13.0 years (9 - 17)	6 months – 36 months: M = 46% F = 54% 3 years – < 9 years: M = 54% F = 46% 9 years – < 18 years: M = 39% F = 61%

Abbreviations: aTIV = adjuvanted Trivalent Influenza (FLUAD®); F = Female; Immunosupp. = immunosuppressive conditions; IM = Intramuscular; M = Male; Non-adj = nonadjuvanted; Med. Cond. = medical conditions; TIV = Trivalent Influenza Vaccine

[1] Number of subjects enrolled

[2] Safety database included 3646 of the 3647 enrolled subjects

*Data from FOCLIVIA®

** Subjects in the primed groups received at least two previous doses of an H5N3 vaccine.

***At Day 1, subjects received a single 0.5 mL IM injection of TIV or placebo, followed by two 0.5 mL IM injections, administered 3 weeks apart (Day 22 and Day 43), of FOCLIVIA® or aTIV

14.4 Immunogenicity

Homologous humoral immune responses (against the H5N1 strain in the vaccine) following two doses of vaccine given 21 days apart are described. Persistence of immune responses at 6 or 12 months after vaccination, and responses to a booster vaccine at that time, are also presented. Heterologous, cross-reactive humoral immune responses (against H5N1 strains not contained in the vaccine) are summarized following the primary and booster vaccine administration. Additionally, evidence supporting long-term immune memory, and evaluations of alternative vaccination schedules and of subjects with underlying medical or immunosuppressive conditions are described.

Immunogenicity response is presented as the seroprotection rate, seroconversion rate and geometric mean ratio.

Seroprotection rate is defined as the proportion of subjects with an antibody titer ≥ 1:40 for hemagglutination inhibition (HI) assay, and an area ≥ 25 mm2 for single radial hemolysis (SRH).

Seroconversion rate is defined as the proportion of subjects with either:

- A negative pre-vaccination HI titer of <1:10, and a protective post-vaccination HI titer of ≥ 1:40; or a positive pre-vaccination HI titer (≥1:10), and at least a 4-fold increase in post-vaccination HI titer; or
- A negative pre-vaccination SRH area of ≤ 4 mm2, and a protective post-vaccination SRH area of ≥ 25 mm2; or a positive pre-vaccination SRH area, and at least a 50% increase in SRH area post-vaccination.

Geometric mean ratio is defined as the ratio of the post-vaccination geometric mean titer divided by the pre-vaccination geometric mean titer.

The CHMP (Committee for Proprietary Medicinal Products; CHMP/BWP/214/96) criteria applicable to these parameters are defined as follows:

- Seroprotection rate: >70% for subjects 18-60 years of age, and >60% for subjects above 60 years of age;
- Seroconversion rate: >40% for subjects 18-60 years of age, and >30% for subjects above 60 years of age;
- Geometric mean ratio: >2.5 for subjects 18-60 years of age, and >2.0 for subjects above 60 years of age.

In addition, neutralizing antibodies have been measured using the microneutralization (MN) assay. A 4-fold increase in neutralizing antibody titers above baseline have been used as an indication of immunogenicity response.

Although CHMP criteria are not specifically defined for pediatric subjects, the same criteria were used as for adults 18-60 years of age

Immunogenicity of FOCLIVIA® in Adults 18 to 60 years of age

The seroprotection rate, seroconversion rate and geometric mean ratio for anti-HA antibodies to A/Vietnam/1194/2004 (H5N1) were measured by SRH and HI assay in adult studies V87P1, V87P13, and V87_17. The seroprotection rate ranged from 71% (95% CI: 63-78) to 91% (95% CI: 87-95) for SRH and from 61% (95% CI: 53-67) to 73% (95% CI: 65-80) for HI (Table 5). Immune responses by baseline status were also reported for Study V87P13 (Table 6).

Table 5: Immune Reponses 21 Days after Second Vaccination with FOCLIVIA® in Adults 18 to 60 Years of Age (V87P1, V87P13, and V87_17)

Assay	Immune Response	Study V87P1	Study V87P13	Study V87_17
SRH		**N=149**	**N=197**	**N=153**
	Seroprotection rate (95%CI)	85% (79-91)	91% (87-95)	71% (63-78)
	Seroconversion rate (95%CI)	85% (78-90)	78% (72-84)	76% (68-82)
	Geometric mean ratio (95%CI)	7.74 (6.6-9.07)	4.03 (3.54-4.59)	5.66 (4.76-6.72)
HI		**N=151**	**N=195**	**N=151**
	Seroprotection rate (95%CI)	73% (65-80)	61% (53-67)	64% (55-71)
	Seroconversion rate (95%CI)	73% (65-80)	56% (49-63)	63% (55-71)
	Geometric mean ratio (95%CI)	16 (12-21)	7.1 (5.52-9.14)	10 (7.15-15)

Abbreviations: SRH = single radial hemolysis; CI = confidence interval; HI = hemagglutination inhibition

Table 6: Immune Reponses 21 Days after Second Vaccination with FOCLIVIA® in Adults 18 to 60 Years of Age (Study V87P13)

Assay	Immune Response	Study V87P13	Study V87P13
SRH		**N=69**	**N=128**
	Baseline Serostatus	< 4 mm^2	≥ 4 mm^2
	Seroprotection rate (95%CI)	87% (77-94)	94% (88-97)
	Seroconversion rate (95%CI)	87% (77-94)	73% (65-81)
	Geometric mean ratio (95%CI)	8.87 (7.09-11)	2.71 (2.38-3.08)
HI		**N=177**	**N=18**
	Baseline Serostatus	HI titer <1:10	HI titer ≥1:10
	Seroprotection rate (95%CI)	58% (50-65)	89% (65-99)
	Seroconversion rate (95%CI)	58% (50-65)	44% (22-69)
	Geometric mean ratio (95%CI)	7.95 (6.1-10)	3.01 (1.44-6.26)

Abbreviations: SRH = single radial hemolysis; CI = confidence interval; HI = hemagglutination inhibition

Microneutralization results for these adult studies are consistent with results obtained with the SRH assay. A total of 83% (95% CI: 77-89; Study V87P1), 65% (95% CI: 58-72; Study V87P13), and 65% (95% CI: 57-73; Study V87_17) of adult subjects 18 to 60 years of age achieved an at least 4-fold increase of MN titer above baseline.

In Study V87P11 conducted in 343 participants (194 adults and 149 elderly subjects), immune responses against the homologous A/turkey/Turkey/1/2005 strain as assessed by SRH, HI and MN assays were consistent with the results obtained from the key studies. As measured by the SRH assay, 91% (95% CI: 85-94) of adult subjects achieved seroprotection, 85% (95% CI: 79-90) achieved seroconversion, and the geometric mean ratio was 6 (95% CI: 5.2-6.9). As measured by the HI assay, 70% (95% CI: 63-77) of adult subjects achieved seroprotection, 69% (95% CI: 62-76) achieved seroconversion, and the geometric mean ratio was 19 (95% CI: 14-26). A total of 93% (95% CI: 89-96) of adult subjects achieved an at least 4-fold increase of MN titer above baseline. Persistence of antibodies after primary vaccination in this population was assessed by HI, SRH, and MN assays. Compared to the antibody levels obtained at Day 43 after completion of primary vaccination schedules, antibody levels at Day 202 were reduced by 1/5 to 1/2 from their prior levels

Immunogenicity of FOCLIVIA® in Adults >60 years of age

The seroprotection rate, seroconversion rate and the geometric mean ratio for anti-HA antibodies to FOCLIVIA® (A/Vietnam/1194/2004 (H5N1)) in subjects > 60 years of age (limited number of subjects were above 70 years of age) measured by SRH and HI assay were assessed in clinical studies V87P1, V87P13 and V87_17. The results are presented in Table 7. Table 8 presents the immune responses by baseline status for Study V87P13.

Table 7: Immune Reponses 21 Days after Second Vaccination with FOCLIVIA® in Elderly Subjects > 60 Years of Age (Studies V87P1, V87P13, and V87_17)

Assay	Immune Response	Study V87P1	Study V87P13	Study V87_17
SRH		**N=84**	**N=209**	**N=121**
	Seroprotection rate (95% CI)	80% (70-88)	82% (76-87)	69% (60-77)
	Seroconversion rate (95% CI)	70% (59-80)	63% (56-69)	67% (58-75)
	Geometric mean ratio (95% CI)	4.96 (3.87-6.37)	2.9 (2.53-3.31)	3.47 (2.71-4.43)
HI		**N=81**	**N=203**	**N=121**
	Seroprotection rate (95% CI)	75% (64-84)	57% (50-64)	64% (55-73)
	Seroconversion rate (95% CI)	67% (55-77)	50% (43-57)	62% (52-71)
	Geometric mean ratio (95% CI)	9.52 (6.55-14)	5.15 (4.15-6.4)	7.69 (4.99-12)

Abbreviations: SRH = single radial hemolysis; CI = confidence interval; HI = hemagglutination inhibition

Table 8: Immune Reponses 21 Days after Vaccination with FOCLIVIA® in Elderly Subjects > 60 Years of Age by Baseline Status (Study V87P13)

Assay	Immune Response	Study V87P13	Study V87P13
SRH		**N=66**	**N=143**
	Baseline Serostatus	< 4 mm^2	≥ 4 mm^2
	Seroprotection rate (95% CI)	82% (70-90)	82% (75-88)
	Seroconversion rate (95% CI)	82% (70-90)	54% (45-62)
	Geometric mean ratio (95% CI)	8.58 (6.57-11)	1.91 (1.72-2.12)
HI		**N=166**	**N=37**
	Baseline Serostatus	HI titer <1:10	HI titer ≥1:10

	Seroprotection rate (95% CI)	49% (41-57)	92% (78-98)
	Seroconversion rate (95% CI)	49% (41-57)	54% (37-71)
	Geometric mean ratio (95% CI)	5.5 (4.29-7.05)	4.2 (2.59-6.81)

Abbreviations: SRH = single radial hemolysis; CI = confidence interval; HI = hemagglutination inhibition

Microneutralization results for these studies are consistent with results obtained with the SRH assay. A total of 58% (95% CI: 47-69; Study V87P1), 55% (95% CI: 48-62; Study V87P13), and 58% (95% CI: 49-67; Study V87_17) of elderly subjects > 60 years of age achieved an at least 4-fold increase of MN titer above baseline. The MN results, similar to SRH results, demonstrated a strong immune response after completion of priming vaccination series in a population of elderly subjects.

In Study V87P11 conducted in 343 participants (194 adults and 149 elderly subjects), immune responses against the homologous A/turkey/Turkey/1/2005 strain were also assessed by the SRH and HI assay, and were consistent with the results obtained from the key studies. MN results against homologous A/turkey/Turkey/1/2005 indicate that 68% (95%CI: 59 75) of subjects achieved MN titers ≥1:40, and 81% (95% CI: 74 87) of subjects achieved an at least 4-fold increase of MN titer above baseline. Immune response to vaccination assessed by MN assay is similar to SRH results.

Based on data obtained from Studies V87P1, V87P11 and V87P13, persistence of antibodies after primary vaccination in elderly subjects, as assessed by HI, SRH, and MN tests, were reduced to 20 to 50% of their post-vaccination level at Day 202 as compared to Day 43 after completion of primary vaccination schedules. Up to 50% (N=33) of the elderly subjects (>60 years) immunized with homologous aH5N1 A/Vietnam/1194/2004 strain or homologous aH5N1 A/turkey/Turkey/1/2005 strain had an antibody titer ≥1:40 at six months.

Booster vaccination

A third (booster) dose of FOCLIVIA® was administered 6 months after the primary vaccination schedule in Studies V87P1 and V87P2. The seroprotection rates, seroconversion rates and the geometric mean ratios as measured by SRH assays are presented in Table 9.

Table 9: Booster Immune Response 21 Days after Third Vaccination in Adult Subjects 18 to 60 years of Age and Elderly Subjects > 60 Years of Age (Studies V87P1, V87P2)

Assay	Immune Response	Study V87P1 Adults	Study V87P2 Adults	Study V87P1 Elderly
SRH		**N=71**	**N=13**	**N=38**
	Seroprotection rate (95% CI)	89% (79-95)	85% (55-98)	84% (69-94)
	Seroconversion rate (95% CI)	83% (72-91)	69% (39-91)	63% (46-78)
	Geometric mean ratio (95% CI)	5.96 (4.72-7.53)	2.49 (1.56-3.98)	5.15 (3.46-7.66)
HI		**N=71**	**N=13**	**N=37**
	Seroprotection rate (95% CI)	83% (72-91)	85% (55-98)	92% (78-98)
	Seroconversion rate (95% CI)	73% (61-83)	77% (46-95)	51% (34-68)
	Geometric mean ratio (95% CI)	11 (7.59-16)	10 (3.74-28)	5.02 (2.8-8.98)

Abbreviations: SRH = single radial hemolysis; CI = confidence interval; HI = hemagglutination inhibition

Cross-reactivity

Immunogenicity analyses were carried out against heterologous strains in Studies V87P1, V87P13, V87_17 and Studies V87P12 and V87P3.

An overview of the immune responses in the SRH and HI assays after 2 injections of H5N1 (A/Vietnam/1194/2004) (Clade 1) against the heterologous Clade 2 strains (A/Indonesia/5/2005 and A/turkey/Turkey/1/2005) is presented in Table 10 and Table 11. Heterologous immune response against

A/turkey/Turkey/1/2005 (Clade 2.2) and A/Indonesia/5/2005 (Clade 2.1) was detectable in all studies, indicating cross-reactivity of the Clade 1 vaccine against Clade 2 strains.

Heterologous immune responses against A/Indonesia/5/2005 (Clade 2.1) and A/Vietnam/1194/2004 (Clade 1) strains were also detectable in Study V87P11 after the second vaccination, indicating cross-reactivity of the Clade 2.2. vaccine against Clade 2.1 and Clade 1 strains (Table 12).

Table 10: Immunogenicity to Heterologous Strains 21 Days after Second Vaccination with FOCLIVIA® aH5N1 (A/Vietnam/1194/2004) in Adult (18 to 60 Years of Age) Subjects (Studies V87P1 and V87P13)

Assay	Immune Response	Study V87P1		Study V87P13
		A/turkey/Turkey/1/2005	A/Indonesia/5/2005	A/turkey/Turkey/1/2005
SRH		**N=70**	**-**	**N=197**
	Seroprotection rate (95%CI)	70% (58-80)	-	59% (52-66)
	Seroconversion rate (95%CI)	NA*	-	49% (42-56)
	Geometric mean ratio (95%CI)	NA*	-	2.37 (2.1-2.67)
HI		**N=69**	**N=70**	**N=197**
	Seroprotection rate (95%CI)	36% (25-49)	21% (13-33)	23% (18-30)
	Seroconversion rate (95%CI)	NA*	NA*	19% (14-25)
	Geometric mean ratio (95%CI)	NA*	NA*	1.92 (1.64-2.25)

* baseline not tested

Abbreviations: SRH = single radial hemolysis; CI = confidence interval; HI = hemagglutination inhibition

Table 11: Immunogenicity to Heterologous Strains 21 Days after Second Vaccination with FOCLIVIA® aH5N1 (A/Vietnam/1194/2004) in Adult (18 to 60 Years of Age) Subjects (Studies V87P12 and V87P3)

Assay	Immune Response	Study V87P12	Study V87P3	
		A/turkey/Turkey/1/2005	A/turkey/Turkey/1/2005	A/Indonesia/5/2005
SRH		**N=60**	**N=29**	-
	Seroprotection rate (95% CI)	65% (52-77)	90% (73-98)	-
	Seroconversion rate (95% CI)	65% (52-77)	86% (68-96)	-
	Geometric mean ratio (95% CI)	4.51 (3.63-5.61)	7.67 (6.09-9.67)	-
HI		**N=60**	**N=29**	**N=29**
	Seroprotection rate (95% CI)	28% (17-41)	24% (10-44)	21% (8-40)
	Seroconversion rate (95% CI)	28% (17-41)	21% (8-40)	10% (2-27)
	Geometric mean ratio (95% CI)	2.3 (1.67-3.16)	1.98 (1.22-3.21)	1.3 (0.85-1.98)

Abbreviations: SRH = single radial hemolysis; CI = confidence interval; HI = hemagglutination inhibition

Table 12: Immunogenicity to Heterologous Strain 21 Days after Second Vaccination with aH5N1 (A/turkey/Turkey/1/2005) in Adult (18 to 60 Years of Age) and Elderly (>60 Years of Age) Subjects (Study V87P11)

Assay	Immune Response	Study V87P11 Adults		Study V87P11 Elderly	
		A/Indonesia/ 5/2005	A/Vietnam/ 1194/2004	A/Indonesia/ 5/2005	A/Vietnam/ 1194/2004
SRH assay		N=182		N=132	
	Seroprotection rate (95% CI)	83% (77-88)	62% (54-69)	61% (52-69)	45% (37-54)
	Seroconversion rate (95%CI)	79% (72-85)	60% (53-68)	64% (56-73)	44% (35-53)
	Geometric mean ratio (95% CI)	6.24 (5.44-7.16)	4.45 (3.85-5.14)	3.87 (3.31-4.53)	3.03 (2.56-3.58)
HI assay		N=194		N=148	
	Seroprotection rate (95%CI)	50% (43-57)	47% (40-55)	34% (26-42)	39% (31-48)
	Seroconversion rate (95% CI)	49% (42-56)	44% (37-51)	32% (25-41)	34% (26-42)
	Geometric mean ratio (95% CI)	4.71 (3.74-5.93)	4.25 (3.36-5.37)	2.69 (2.18-3.32)	2.8 (2.2-3.55)

Abbreviations: SRH = single radial hemolysis; CI = confidence interval; HI = hemagglutination inhibition

The following information is provided as supportive data for potential influenza pandemic situations:

Long-term immune memory:

In Study V87P3 adult subjects (N=12) aged 18-65 years primed 6-8 years previously with 2 doses of MF59-adjuvanted H5N3 vaccine/A/Duck/Singapore/1997, were administered 2 booster doses of H5N1 A/Vietnam/1194/2004. After the first dose, which mimicked pre-pandemic priming plus a single heterologous booster dose, SRH assay results revealed seroprotection and seroconversion rates of 100% (95% CI: 74-100) and an 18-fold increase in SRH area (GMR).

Alternative vaccination schedules:

In Study V87P12 which evaluated 4 different vaccination schedules of aH5N1, in 240 healthy subjects (18-60 years). Subjects achieved high levels of antibodies 3 weeks after the 2nd vaccination as evaluated with SRH. SRH seroprotection rates ranged from 86% to 98%, seroconversion rated from 64% to 90%, and GMR ranged from 2.92 to 4.57. The magnitude of immune response was lower in the group with an interval of only 1 week between the two doses, versus the groups with longer interval schedules.

Subjects with underlying medical or immunosuppressive conditions:

Immunogenicity of aH5N1 (A/turkey/Turkey/1/2005) was evaluated in adult (18 - 60 years of age) and elderly (> 60 years of age) subjects with underlying medical conditions (Study V87_25) or immunosuppressive conditions (Study V87_26), in comparison to healthy adults (18 - 60) and elderly (> 60 years of age).

In these studies, aH5N1 was shown to be immunogenic in subjects with underlying medical or immunosuppressive conditions by inducing an increase in antibody titers (HI, SRH and MN) following either one or two vaccinations. In both studies the immune response was lower in subjects with underlying medical or immunosuppressive conditions compared with healthy subjects. Although an increase in immune response was seen at Day 22 following a single vaccination, the data support the administration of two doses.

Immunogenicity of FOCLIVIA® in Children and Adolescents 6 months to less than 18 years of age

In pediatric Study V87P6 two FOCLIVIA® doses were administered three weeks apart, with a third dose administered 12 months following the first dose. Three weeks after the 2nd vaccination (Day 43), subjects in all age groups (i.e. toddlers: 6 to < 36 months, children: 3 to < 9 years, and adolescents: 9 to < 18 years) achieved high levels of antibodies to FOCLIVIA® as evaluated by SRH and HI assays. Immunogenicity results are presented in Table 13.

Table 13: Immunogenicity 21 Days after the Second Vaccination with FOCLIVIA® in Children 6 Months to < 18 years of Age (Study V87P6)

		Toddlers (6 to < 36 months)	Children (3 to < 9 years)	Adolescents (9 to < 18 years)
SRH assay		**N=133**	**N=91**	**N=90**
	Seroprotection rate (95% CI) Day 43	100% (97-100)	100% (96-100)	100% (96-100)
	Seroconversion rate (95% CI) Day 43	98% (95-100)	100% (96-100)	99% (94-100)
	Geometric mean ratio (95% CI) Day 43 to Day 1	16 (14-18)	15 (13-17)	14 (12-16)
		N=131	**N=91**	**N=89**
HI assay	Seroprotection rate (95% CI) Day 43	97% (92-99)	97% (91-99)	89% (80-94)
	Seroconversion rate (95% CI) Day 43	97% (92-99)	97% (91-99)	89% (80-94)
	Geometric mean ratio (95% CI) Day 43 to Day 1	129 (109-151)	117 (97-142)	67 (51-88)

Abbreviations: SRH = single radial hemolysis; CI = confidence interval; GMR = geometric mean ratio; HI = hemagglutination inhibition

Almost all pediatric subjects achieved MN titers ≥1:40 (99% of subjects in each age group). An at least 4-fold increase in MN titer above baseline was achieved by 99% (95% CI: 96-100) of toddlers, 98% (95% CI: 92-100) of children, and 97% (95% CI: 91-99) of adolescents.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicity: Non-clinical data obtained with FOCLIVIA® and with seasonal influenza vaccine containing MF59C.1 adjuvant reveal no special hazard for humans based on conventional studies of repeat dose toxicity, local tolerance, female fertility, and reproductive and developmental toxicity (through to the end of the lactation period.

Carcinogenicity and Genotoxicity: Carcinogenic and genotoxicity potential were not assessed because

these studies are not appropriate for a vaccine.

Reproductive and Developmental Toxicology: In a reproductive and developmental toxicity study, the effect of FOCLIVIA® on embryo-fetal and post-natal development was evaluated in pregnant rabbits. Animals received three intramuscular doses of vaccine before mating and two additional doses during gestation. Although peak antibody response was not sustained throughout pregnancy, there was adequate exposure of rabbits to the vaccine. On a body weight basis, each 0.5 mL dose administered to rabbits (4 kg) was approximately 25 times the adult dose for humans (50 kg). No adverse effects on mating, female fertility, pregnancy, embryo-fetal development, or post-natal development were observed. There were no vaccine-related fetal malformations or other evidence of teratogenesis.

17 SUPPORTING PRODUCT MONOGRAPHS

1. FLUAD® Pediatric / FLUAD®, Suspension, 15 mcg / 0.5 mL A(H1N1), 15 mcg / 0.5 mL A(H3N2), 15 mcg / 0.5 mL Strain B, Control No. 228033, Product Monograph, Seqirus UK Limited. June 17, 2019.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

FOCLIVIA®

Pandemic Influenza Vaccine, suspension for injection

Read this carefully before you are given **FOCLIVIA®**. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **FOCLIVIA®**.

What is FOCLIVIA used for?

FOCLIVIA® is a vaccine intended to be given to prevent influenza (flu) in an officially declared pandemic situation in individuals 6 months of age and older.

Pandemic flu is a type of influenza that happens infrequently, but spreads rapidly around the world. It is caused by a new influenza virus to which people have no prior immunity. The signs of pandemic flu are similar to those of ordinary flu but may be more serious.

How does FOCLIVIA work?

Like other influenza vaccines, FOCLIVIA® causes the body to produce antibodies against the virus. However, FOCLIVIA® contains an additional ingredient, "an adjuvant," that helps to boost your body's production of antibodies. This means that when your body is exposed to the flu virus, your body is more effective at defending itself.

The vaccine is given by injection with a needle in the upper arm and will require two doses given three weeks apart. Individuals may not be optimally protected until after receiving the second dose of the vaccine.

You cannot catch influenza from the vaccine, since it only contains portions of the virus, and not the whole live virus.

As with all vaccines, FOCLIVIA® may not fully protect all persons who are vaccinated.

What are the ingredients in FOCLIVIA®?

Medicinal ingredients:

Each 0.5 mL dose of the vaccine contains 7.5 mcg haemagglutinin (HA) from the following influenza strain:

- A/Vietnam/1194/2004 (H5N1) strain.

Non-medicinal ingredients:

- calcium chloride dihydrate,
- cetyltrimethylammonium bromide (CTAB)*,
- disodium phosphate dihydrate,
- egg proteins, including ovalbumin*,
- formaldehyde*,
- hydrocortisone*,
- kanamycin sulphate*,
- magnesium chloride hexahydrate,

- neomycin sulphate*,
- potassium chloride,
- potassium dihydrogen phosphate,
- sodium chloride,
- thimerosal**,
- water for injections

*Residuals
**Thimerosal is included in multi-dose vials only.

Adjuvant (MF59C.1): Citric acid monohydrate, polysorbate 80, sodium citrate dihydrate, sorbitan trioleate, squalene.

The tip cap and plungers of the pre-filled syringe and the multi-dose vial stopper are not made with natural rubber latex. FOCLIVIA® is considered safe for use in persons with latex allergies.

FOCLIVIA® comes in the following dosage forms:

FOCLIVIA® is supplied as a suspension for intramuscular injection in either a 0.5 mL single-dose, pre-filled syringe or a 5 mL multi-dose vial.

Do not use FOCLIVIA®:

if you or your child:

- have experienced serious allergic reaction (i.e. life-threatening) to any of the constituents of FOCLIVIA®,
- are allergic to:
  kanamycin sulfate (antibiotic), neomycin sulfate (antibiotic), formaldehyde, cetyltrimethylammonium bromide, hydrocortisone or polysorbate 80.

  Signs of an allergic reaction may include itchy skin rash, shortness of breath and swelling of the face or tongue.

However, in a pandemic situation, you may still be given the vaccine, provided that medical treatment is available, in case you have an allergic reaction.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you are given FOCLIVIA®. Talk about any health conditions or problems you may have, including if you or your child:

- **have or have had a reaction to vaccination with any of the following:**
  - severe allergic reaction
  - difficulty breathing
  - swelling of the throat
  - fainting or collapse
  - fits or convulsions
  - high temperature (greater than 38.5°C)

- **have an infection or temperature higher than 38.5°C.** Your doctor may decide to delay vaccination until the illness has passed. A minor illness such as a cold is not usually a reason to delay vaccination.
- **have a bleeding problem, bruise easily or use a blood thinning medication**
- **have low immunity due to treatment with certain medicines**
- **have allergies to other medicines or substances**
- **are pregnant or breastfeeding.** Your healthcare professional will be able to discuss the potential risks and benefits of having FOCLIVIA® while you are pregnant or breastfeeding.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with FOCLIVIA®:

- Immunosuppressive or corticosteroid therapies may lower your immune response to this vaccine
- If co-administration with another vaccine is indicated, immunization should be carried out on separate limbs.

How FOCLIVIA® is given:

FOCLIVIA® is given as an injection into a muscle, usually in the upper arm.

Usual dose:

Individuals 6 months of age and older: Two 0.5 mL doses administered with an interval of at least 21 days between doses. It is very important that you return for the second injection, or the vaccine may not work as well.

Overdose:

If you think you have been given too many doses of FOCLIVIA® or have been given it by mistake, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

What are possible side effects from using FOCLIVIA®?

These are not all the possible side effects you may have when receiving FOCLIVIA®. If you experience any side effects not listed here, tell your healthcare professional.

The following are common or very common side effects of FOCLIVIA®. Most of these side effects are mild and disappear within 1-2 days without treatment. Tell your doctor if you or your child have side effects that bother you:

- Injection site pain, reddening, hardening, swelling or bruising
- Headache
- Muscle or joint pain
- Tiredness
- Feeling unwell
- Shivering
- Sweating
- Nausea
- Fever

The following additional side effects were reported commonly or very commonly in children 6 months to 3 years of age:

- Unusual crying
- Irritability
- Sleepiness
- Diarrhea
- Change in eating habits
- Vomiting
- Unusual sweating

The following additional side effects were reported for another influenza vaccine containing the same MF59® adjuvant during the 2009 Influenza A (H1N1) pandemic.

- Swelling of the glands in the neck, armpit or groin (lymphadenopathy)
- Allergic reactions (which may occur immediately):
  - leading to medical emergency with a failure of the circulatory system to maintain adequate blood flow to the different organs (shock) in rare cases,
  - may include symptoms of swelling of the face, lips, tongue or throat.
- Pain situated on the nerve route (neuralgia), abnormalities in the perception of touch, pain, feelings of pins and needles (paraesthesia), fits (convulsions)
- Skin reactions that may spread throughout the body including itchiness of the skin (pruritus), rash and hives (urticaria)
- Muscular weakness and pain in the extremities
- Cough

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
RARE			
Anaphylaxis Difficulty breathing, dizziness, a weak and rapid pulse, skin rash		✓	
Allergic reaction Rash, itching or hives on the skin, swelling of the face, lips, tongue, or other parts of the body		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

If you experience a severe allergic reaction, call the local emergency number or go to the nearest hospital.

Reporting Suspected Side Effects for Vaccines

For the general public: Should you experience a side effect following immunization, please report it to your healthcare professional.

Should you require information related to the management of the side effect, please contact your healthcare professional. The Public Health Agency of Canada, Health Canada and Seqirus cannot provide medical advice.

For healthcare professionals: If a patient experiences a side effect following immunization, please complete the Adverse Events Following Immunization (AEFI) Form appropriate for your province/territory (http://www.phac-aspc.gc.ca/im/aefi-essi-form-eng.php) and send it to your local Health Unit.

Storage:

Store in a refrigerator between 2° to 8°C. Do not freeze. Discard if the vaccine has been frozen. Protect from light. Do not use after the expiration date. Return the multi-dose vial to the recommended storage conditions between uses.

Keep out of reach and sight of children.

If you want more information about FOCLIVIA®:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.seqirus.ca or by calling 1-855-358-8966.

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