ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

HUMENZA suspension and emulsion for emulsion for injection
Pandemic influenza vaccine (H1N1) (split virion, inactivated, adjuvanted)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

HUMENZA consists of two vials: one vial containing the antigen (suspension) and one vial containing the adjuvant (emulsion), which are mixed prior to administration.

After mixing, 1 dose (0.5ml) contains:

Split influenza virus*, inactivated containing antigen equivalent to:
A/California/7/2009 (H1N1)-like strain (NYMC X-179A).....3.8 micrograms**

* propagated in eggs
** expressed in microgram haemagglutinin

This vaccine complies with the WHO recommendation and EU decision for the pandemic.

AF03 adjuvant composed of squalene (12.4 milligrams), sorbitan oleate (1.9 milligrams), polyoxyethylene cetostearyl ether (2.4 milligrams) and mannitol (2.3 milligrams)

The suspension and emulsion, once mixed, form a multidose vaccine in a vial. See section 6.5 for the number of doses per vial.

Excipients:
The vaccine contains 11.3 micrograms thiomersal.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension and emulsion for emulsion for injection.
The antigen is a colourless limpid to opalescent suspension.
The adjuvant is a white opaque emulsion.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prophylaxis of influenza in an officially declared pandemic situation (see sections 4.2 and 5.1).

Pandemic influenza vaccine should be used in accordance with Official Guidance.

4.2 Posology and method of administration

Posology

In the different age groups, there are limited data (adults aged 18 to 60 years), very limited data (adults aged 61 years and over, children aged 6 months to 17 years) or no data (children aged less than 6 months) with HUMENZA as detailed in sections 4.4, 4.8 and 5.1.

Children from 3 years of age, adolescents and adults up to 60 years of age:
One dose of 0.5 ml at an elected date.
Immunogenicity data obtained at three weeks after administration of Humenza in clinical studies suggest that a single dose may be sufficient.
If a second dose is administered there should be an interval of at least three weeks between the first and the second dose.

Elderly above 60 years of age:
One dose of 0.5 ml at an elected date.
A second dose of vaccine should be given after an interval of at least three weeks.

Children from 6 months of age to less than 3 years of age:
One half-dose of 0.25 ml at an elected date.
Immunogenicity data obtained in a limited number of children aged 6-35 months show that there is a further immune response to a second half-dose of 0.25 ml administered after an interval of three weeks.
The use of a second half-dose should take into consideration the information provided in sections 4.4, 4.8 and 5.1.

Children below 6 months of age:
Vaccination is currently not recommended in this age group.

For further information, see section 5.1.

It is recommended that subjects who receive a first dose of HUMENZA, complete the vaccination course with HUMENZA (see section 4.4).

Method of administration

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

For instructions for preparation, see section 6.6.

4.3 Contraindications

History of an anaphylactic (i.e. life-threatening) reaction to any of the constituents or trace residues (ovalbumin, egg and chicken proteins, neomycin, octoxinol-9, formaldehyde). If vaccination is considered to be necessary, facilities for resuscitation should be immediately available in case of need.

See section 4.4. for Special warnings and special precautions for use.

4.4 Special warnings and precautions for use

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, to thiomersal, and to residues (ovalbumin, egg and chicken proteins, neomycin, octoxinol-9, formaldehyde).

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

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

HUMENZA should under no circumstances be administered intravascularly.

There are no data with HUMENZA using the subcutaneous route. Therefore, healthcare providers need to assess the benefits and potential risks of administering the vaccine in individuals with thrombocytopenia or any bleeding disorder that would contraindicate intramuscular injection unless the potential benefit outweighs the risk of bleedings.

There are no data on administration of AF03-adjuvanted vaccines before or following other types of influenza vaccines intended for pre-pandemic or pandemic use.

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

A protective immune response may not be elicited in all vaccinees (see section 5.1).

Very limited data in children aged 6 to 35 months (N=96) who received two doses of 0.25 ml (half of the adult dose) with an interval of 3 weeks between doses indicate an increase in the rates of injection site reactions and general symptoms (see section 4.8.). In particular rates of fever (axillary temperature ≥38°C) may increase considerably after the second dose. Therefore, monitoring of temperature and measures to lower fever (such as antipyretic medication as seems clinically necessary) are recommended in young children (e.g. up to approximately 8 years of age) after each vaccination.

There are very limited safety and immunogenicity data available from clinical studies with HUMENZA in adults aged over 60 years of age.

There are no safety, immunogenicity or efficacy data to support interchangeability of HUMENZA with other H1N1 pandemic vaccines.

4.5 Interaction with other medicinal products and other forms of interaction

There are no data on co-administration of HUMENZA with other vaccines. However, if co-administration with another vaccine is considered, immunisation should be carried out on separate limbs. It should be noted that the adverse reactions may be intensified.

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

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

4.6 Pregnancy and lactation

No data have been generated in pregnant or lactating women with the vaccine HUMENZA or with any other vaccine containing adjuvant AF03.

A reproductive and developmental toxicity study conducted in rabbits with HUMENZA showed no effects on embryo fetal development.

The use of HUMENZA may be considered during pregnancy and lactation if this is thought to be necessary, taking into account official recommendations.

4.7 Effects on ability to drive and use machines

Some of the effects mentioned under section 4.8 “Undesirable Effects” may affect the ability to drive or use machines.

4.8 Undesirable effects

- Clinical trials

Adults and elderly:

In an open-label clinical trial, two doses (0.5 ml) of HUMENZA have been administered at a 3-week interval in 153 subjects (99 adults and 54 elderly).

Local and systemic reactions occurred within 7 days following any vaccine administration. These reactions were usually resolved spontaneously within 1 to 3 days after onset. The severity of these reactions was from grade 1 (mild) to grade 2 (moderate). The rate of grade 3 (severe) reactions was overall low (≤ 2%).

The most frequent reaction was injection site pain.

Overall, reactions were more frequent in adults than in elderly and less frequent after the second dose in both age groups.

Adverse reactions reported following any vaccination are listed below 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)

Nervous system disorders
- Very common: headache

Musculoskeletal and connective tissue disorders
- Very common: myalgia

General disorders and administration site conditions
- Very common: injection site pain
- Common: malaise, shivering, fever, injection site reactions such as induration, erythema, swelling, ecchymosis.

Children and adolescent (from 3 to 17 years of age):
In an open-label clinical trial, two doses (0.5 ml) of HUMENZA have been administered at a 3-week interval in 50 children from 3 to 8 years of age and 49 adolescents from 9 to 17 years of age. The safety has been assessed after each administration.

Overall, reactions were more frequent in children and adolescents than in adults and elderly.

Local and systemic reactions occurred within 7 days following any vaccine administration. These reactions were usually resolved spontaneously within 1 to 3 days after onset.

The severity of the local and systemic reactions was mainly from grade 1 (mild) to grade 2 (moderate). The rate of grade 3 (severe) reactions was overall low (from 2 to 14% in children from 3 to 8 years of age and from 2 to 8.2% in adolescents from 9 to 17 years of age).

In children from 3 to 8 years of age, the most frequent reactions were injection site pain and injection site erythema. Overall, a higher frequency of injection site reactions and fever was reported in this age group compared to the adolescents. Moreover, a higher frequency of fever and headache was reported after the second dose than after the first dose.

In adolescents from 9 to 17 years of age, the most frequent reactions were injection site pain and headache. A higher frequency of headache was reported in this age group compared to the children, adults and elderly.

Percentages of subjects who reported the following adverse reactions after each dose are provided by age group in the table below:

	Children (N=50) 3 to 8 years of age		**Adolescents (N=49) 9 to 17 years of age**	
	1st dose	2nd dose	1st dose	2nd dose
Injection site pain	80.0 %	74.0%	79.6%	67.3%
Injection site erythema	36.0 %	38.0%	22.4%	22.4%
Injection site swelling	20.0%	18.0%	12.2%	12.2%
Injection site induration	18.0%	10.0%	10.2%	12.2%
Injection site ecchymosis	18.0%	12.0%	4.1%	2.0%
Fever (≥ 38°C)	4.0%	20.0%	6.1%	6.1%
Headache	20.0%	32.0%	57.1%	42.9%
Malaise	20.0%	36.0%	36.7%	32.7%
Myalgia	32.0%	24.0%	36.7%	32.7%
Shivering	16.0%	18.0%	26.5%	26.5%

Regarding unsolicited reactions after any vaccination, injection site warmth (4%) was reported in children from 3 to 8 years of age and oropharyngeal pain (6.1%) was reported in adolescents from 9 to 17 years of age.

Children from 6 to 35 months of age:
In an open-label clinical trial, two half-doses (0.25 ml) of HUMENZA have been administered at a 3-week interval in 48 children from 6 to 11 months of age and in 48 children from 12 to 35 months of age.

Local and systemic reactions occurred within 7 days following any vaccine administration. These reactions were usually resolved spontaneously within 1 to 3 days after onset.

The severity of the local and systemic reactions was mainly from grade 1 (mild) to grade 2 (moderate). The rate of grade 3 (severe) reactions was overall low (from 6.5 to 8.3% in children from 6 to 11 months of age and from 8.3 to 12.5% in children from 12 to 35 months of age).

Overall, local and systemic reactions were less frequently observed in children from 6 to 35 months of age than in children from 3 to 8 years, except fever which was more frequently observed in children from 6 to 23 months. Overall, systemic reactions were more frequently reported in children from 6 to 11 months compared to children from 12 to 23 months.

Percentages of subjects who reported the following adverse reactions after each dose are provided by age group in the table below:

	Children (N=48) 6 to 11 months		**Children (N=48) 12 to 35 months**			
	1st dose	2nd dose	1st dose		2nd dose	
Injection site pain/tenderness	18.8%	28.3%	50.0%		29.2%	
Injection site erythema	10.4%	19.6%	14.6%		33.3%	
Injection site swelling	8.3%	6.5%	2.1%		12.5%	
Injection site induration	8.3%	21.7%	12.5%		12.5%	
Injection site ecchymosis	2.1%	4.3%	6.3%		6.3%	
			12 to 23 months		**24 to 35 months**	
			1st dose	2nd dose	1st dose	2nd dose
Fever (≥ 38°C)	8.3%	32.6%	28.6%	7.1%	0.0%	11.8%
Headache	-	-	-	-	2.9%	5.9%
Malaise	-	-	-	-	17.6%	17.6%
Myalgia	-	-	-	-	11.8%	17.6%
Shivering	-	-	-	-	5.9%	17.6%
Vomiting	25.0%	23.9%	7.1%	0.0%	-	-
Abnormal crying	39.6%	37.0%	14.3%	14.3%	-	-
Drowsiness	22.9%	30.4%	14.3%	28.6%	-	-
Appetite lost	33.3%	30.4%	42.9%	21.4%	-	-
Irritability	45.8%	50.0%	28.6%	28.6%	-	-

Regarding unsolicited reactions after any vaccination, diarrhoea (4.3 %) was reported in children from 6 to 11 months of age and cough (4.2 %) was reported in children from 12 to 35 months of age.

- Post-marketing surveillance

From post marketing surveillance with interpandemic trivalent vaccines, the following adverse events have been reported very rarely, even if an exact incidence rate cannot be precisely calculated:

Blood and lymphatic system disorders:
Transient thrombocytopenia, transient lymphadenopathy

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

Nervous system disorders:
Neuralgia, paraesthesia, febrile convulsions, neurological disorders, such as encephalomyelitis, neuritis and Guillain-Barré syndrome

Vascular disorders:
Vasculitis associated in very rare cases with transient renal involvement

Skin and subcutaneous tissue disorders:
Generalised skin reactions including pruritus, urticaria or non-specific rash

This medicinal product contains thiomersal (an organomercuric compound) as a preservative and therefore, it is possible that sensitisation reactions may occur (see section 4.4).

4.9 Overdose

No case of overdose have been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Influenza vaccines, ATC code: J07BB02.

This medicinal product has been authorised under a so-called "conditional approval" scheme.
This means that further evidence on this medicinal product is awaited.
The European Medicines Agency will review any new information on the medicine and this Summary of Product Characteristics will be updated as necessary.

This section describes the clinical experience with HUMENZA following administration of one or two vaccine doses (0.5 ml or 0.25 ml) at a 3-week interval.
The immunogenicity 21 days after each dose has been assessed and is presented below for each age group according to the seroprotection rate, the seroconversion rate and the seroconversion factor, using haemagglutination inhibiting (HI) method.
The seroprotection rate corresponds to the proportion of subjects achieving a post-vaccination titer ≥1:40.
The seroconversion rate corresponds to the proportion of subjects with a pre-vaccination titer <1:10 achieving a post-vaccination titer ≥1:40, or the proportion of subjects with a ≥four-fold increase from pre- to post-vaccination titer.
The seroconversion factor corresponds to the geometric mean of individual ratios (post-/pre-vaccination titers).

For all age groups:
- Immunogenicity results observed with the seroneutralisation (SN) method reflect those observed with HI method.
- No data on antibody persistence are currently available.

<u>Adults (from 18 to 60 years of age):</u>
In a clinical trial, the immunogenicity 21 days after each injection of HUMENZA given 21 days apart has been assessed in 99 adults.

The seroprotection rate, the seroconversion rate and the seroconversion factor, using haemagglutination inhibiting (HI) method, were as follows:

	Adults 18 to 60 years of age	
	Total enrolled subjects N= 99	**Seronegative subjects prior to vaccination** N= 55
21 days after 1st dose		
Seroprotection rate* % [95% CI]	97.0 % [91.4; 99.4]	94.5 % [84.9; 98.9]
Seroconversion rate** % [95% CI]	93.9 % [87.3; 97.7]	94.5 % [84.9; 98.9]
Seroconversion factor*** [95% CI]	76.0 [56.6; 102]	94.0 [64.5; 137]
21 days after 2nd dose		
Seroprotection rate* % [95% CI]	100 % [96.3; 100]	100 % [96.3; 100]
Seroconversion rate** % [95% CI]	99.0 % [94.4; 100]	100 % [96.3; 100]
Seroconversion factor*** [95% CI]	115 [89.1; 147]	178 [134; 235]

* Proportion of subjects achieving a post-vaccination titer ≥1:40
** For subjects with a pre-vaccination titer <1:10, proportion of subjects with a post-vaccination titer ≥1:40 and for subjects with a pre-vaccination titer ≥1:10, proportion of subjects with a ≥four-fold increase from pre- to post-vaccination titer
*** Geometric mean of individual ratios (post-/pre-vaccination titers)

Elderly (>60 years of age):
In a clinical trial, the immunogenicity 21 days after each injection of HUMENZA given 21 days apart has been assessed in 54 elderly (29 elderly from 61 to 70 years of age, 18 elderly from 71 to 80 years of age and 7 elderly of 81 years of age and over).

The seroprotection rate, the seroconversion rate and the seroconversion factor, using HI method, were as follows:

	Elderly 61 to 70 years of age		Elderly 71 to 80 years of age		Elderly 81 years of age and over	
	Total enrolled subjects N= 29	**Seronegative subjects prior to vaccination** N= 14	**Total enrolled subjects** N= 18	**Seronegative subjects prior to vaccination** N= 7	**Total enrolled subjects** N= 7	**Seronegative subjects prior to vaccination** N= 1
21 days after 1st dose						
Seroprotection rate* % [95% CI]	86.2 % [68.3;96.1]	78.6 % [49.2; 95.3]	77.8 % [52.4;93.6]	42.9 % [9.9; 81.6]	85.7 % [42.1;99.6]	0.0 % Not computed
Seroconversion rate** % [95% CI]	82.8 % [64.2;94.2]	78.6 % [49.2; 95.3]	72.2 % [46.5;90.3]	42.9 % [9.9; 81.6]	42.9 % [9.9;81.6]	0.0 % Not computed
Seroconversion factor*** [95% CI]	22.1 [12.4;39.3]	21.5 [9.42; 49.2]	14.5 [5.93;35.6]	4.20 [1.99; 8.90]	5.94 [1.12;31.6]	1.14 Not computed
21 days after 2nd dose						
Seroprotection rate* % [95% CI]	100 % [88.1;100]	100 % [76.8; 100]	94.4 % [72.7;99.9]	85.7 % [42.1; 99.6]	85.7 % [42.1;99.6]	0.0 % Not computed
Seroconversion rate** % [95% CI]	96.6 % [82.2;99.9]	100 % [76.8; 100]	94.4 % [72.7;99.9]	85.7 % [42.1; 99.6]	57.1 % [18.4;90.1]	0.0 % Not computed
Seroconversion factor*** [95% CI]	39.7 [25.3;62.2]	45.3 [23.1; 88.5]	21.0 [11.1;39.7]	14.5 [5.11; 41.1]	8.41 [1.93;36.7]	2.00 Not computed

* Proportion of subjects achieving a post-vaccination titer ≥1:40

** For subjects with a pre-vaccination titer <1:10, proportion of subjects with a post-vaccination titer ≥1:40 and for subjects with a pre-vaccination titer ≥1:10, proportion of subjects with a ≥four-fold increase from pre- to post-vaccination titer

*** Geometric mean of individual ratios (post-/pre-vaccination titers)

Children and adolescents (from 3 to 17 years of age):

In a clinical trial, the immunogenicity 21 days after each injection of HUMENZA given 21 days apart has been assessed in 50 children from 3 to 8 years of age and 49 adolescents from 9 to 17 years of age.

The seroprotection rate, the seroconversion rate and the seroconversion factor, using HI method, were as follows:

	Children 3 to 8 years of age	Adolescents 9 to 17 years of age	
	Total enrolled subjects N= 50	**Total enrolled subjects** N= 49	**Seronegative subjects prior to vaccination** N= 37
21 days after 1st dose			
Seroprotection rate* % [95% CI]	100 % [92.9; 100]	100 % [92.6; 100]	100 % [90.5; 100]
Seroconversion rate** % [95% CI]	100 % [92.9; 100]	100 % [92.6; 100]	100 % [90.5; 100]
Seroconversion factor*** [95% CI]	124 [99.6; 156]	177 [130; 241]	203 [149; 276]
21 days after 2nd dose			
Seroprotection rate* % [95% CI]	100 % [92.7; 100]	100 % [92.7; 100]	100 % [90.5; 100]
Seroconversion rate** % [95% CI]	100 % [92.7; 100]	100 % [92.6; 100]	100 % [90.5; 100]
Seroconversion factor*** [95% CI]	883 [745; 1046]	527 [393; 706]	745 [620; 895]

* Proportion of subjects achieving a post-vaccination titer ≥1:40
** For subjects with a pre-vaccination titer <1:10, proportion of subjects with a post-vaccination titer ≥1:40 and for subjects with a pre-vaccination titer ≥1:10, proportion of subjects with a ≥ four-fold increase from pre- to post-vaccination titer
*** Geometric mean of individual ratios (post-/pre-vaccination titers)

All children aged from 3 to 8 years were seronegative prior to vaccination.

Children (from 6 to 35 months of age):
In an open-label clinical trial, two half-doses (0.25 ml) of HUMENZA have been administered at a 3-week interval in 48 children from 6 to 11 months of age and in 48 children from 12 to 35 months.

The immunogenicity 21 days after each half-dose (0.25 ml) of HUMENZA in term of the seroprotection rate, the seroconversion rate and the seroconversion factor, using HI method, were as follows:

	Children (6 to 11 months of age)	Children (12 to 35 months of age)
	Total enrolled subjects N= 48	**Total enrolled subjects** N= 48
21 days after 1st dose		
Seroprotection rate* % [95% CI]	95.7 % [85.5; 99.5]	97.8 % [88.5; 99.9]
Seroconversion rate** % [95% CI]	95.7 % [85.5; 99.5]	97.8 % [88.5; 99.9]
Seroconversion factor*** [95% CI]	39.9 [30.8; 51.7]	50.7 [38.1; 67.4]
21 days after 2nd dose		
Seroprotection rate* % [95% CI]	100 % [91.8; 100]	100 % [92.5; 100]
Seroconversion rate** % [95% CI]	100 % [91.8; 100]	100 % [92.5; 100]
Seroconversion factor*** [95% CI]	602 [495; 731]	543 [441; 670]

* Proportion of subjects achieving a post-vaccination titer ≥1:40
** For subjects with a pre-vaccination titer <1:10, proportion of subjects with a post-vaccination titer ≥1:40 and for subjects with a pre-vaccination titer ≥1:10, proportion of subjects with a ≥ four-fold increase from pre- to post-vaccination titer
*** Geometric mean of individual ratios (post-/pre-vaccination titers)

All children aged from 6 to 35 months were seronegative prior to vaccination.

Information from non-clinical studies
A challenge ferret study showed vaccine similar protection after one or two human doses based on lung macroscopic examination, body weight loss (as indicator of disease after challenge) and viral loads in lungs and in the upper respiratory tract.

The ability of one or two administrations of HUMENZA to protect ferrets against infection in the lungs was evaluated. Groups of 7 ferrets were immunized intramuscularly (IM) with one human dose of HUMENZA (3.8 µg of HA and full dose AF03) (at D21) or 2-dose administration of one human dose at 3-week intervals (at D0 and D21) and compared to a control group (AF03 adjuvant diluted in PBS). Four weeks after the last vaccine administration, ferrets were challenged with the wild type homologous strain A/H1N1/Netherlands/602/2009.
A single administration of a human dose of HUMENZA elicited HI titers ≥ 80 and MN (Microneutralization) titers ≥ 160 specific to the vaccinal strain in 100% of vaccinated animals and a two-dose administration regimen markedly increased (at least a 5-fold increase) HI and MN antibody titers. A mean body weight loss of 20% was recorded in control group 4 days after infection. This body weight loss was reduced to ≤ 8% in animals that received 1 or 2 doses of HUMENZA. Four days after challenge, in the control group, 34% of the lungs were affected and presented lung lesions associated with high levels of virus replication in lung tissue (≥ 4.7 TCID50/g tissue).

In ferrets administered with one or two doses of HUMENZA, a significant reduction of lung damages (4 % or 1 % of affected lung, respectively) and of lung viral loads (more than 4 log10 reduction) was achieved resulting in 86% (6 out of 7 ferrets) or 100% of ferrets with no detectable virus in lungs, respectively. The protection against infection in the lungs was associated with vaccine-induced HI titers ≥ 40, a titer described in humans to be associated with protection against seasonal influenza. Viral shedding was assessed by measuring viral replication in both nasal and throat swabs and results demonstrated that HUMENZA was able to consistently reduce the viral load in the upper respiratory tract.

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Available non clinical data obtained with the vaccine HUMENZA or with the same vaccine but with another strain (A/H5N1) revealed no special hazard for humans based on conventional repeat dose toxicity studies, reproductive and developmental toxicity studies and an investigative pneumopathology study.

Repeated injections of the vaccine induced moderate local inflammation in rabbits and no exacerbation of pneumonia after exposure to the parental wild-type virus in monkeys. Rabbits dosed with vaccine, or with AF03 adjuvant alone, showed a slight increase of apoptosis / necrosis in the lachrymal tissues at doses higher than the human dose. Rabbits dams dosed with vaccine pre-mating and during gestation did not show any effects on embryofetal development.

The adjuvant, AF03, was not mutagenic or clastogenic and induced transient inflammatory changes in repeat dose toxicity studies (in rats and rabbits). The reproductive and developmental toxicity studies conducted in rats and rabbits with AF03 did not show any effects on female fertility, pregnancy, embryofetal development or early postnatal development.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Antigen vial:
Thiomersal
Sodium chloride
Potassium chloride
Disodium phosphate dihydrate
Potassium dihydrogen phosphate
Water for injections

Adjuvant vial:
Sodium chloride
Potassium chloride
Disodium phosphate dihydrate
Potassium dihydrogen phosphate
Water for injections

For adjuvant, see section 2.

6.2 Incompatibilities

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

6.3 Shelf life

6 months.
After mixing, HUMENZA should be stored in a refrigerator (2°C-8°C) and should be used within 24 hours.

6.4 Special precautions for storage

Store in a refrigerator (2°C-8°C). Do not freeze.
For storage conditions after opening, see section 6.3.
Keep the vials in the outer carton in order to protect from light.

6.5 Nature and contents of container

One pack containing:
- One pack of 10 vials (type I glass) of 1.5 ml suspension (antigen) with stopper (chlorobutyl).
- One pack of 10 vials (type I glass) of 4.5 ml emulsion (adjuvant) with stopper (chlorobutyl).

Number of doses after mixing the content of antigen vial into the adjuvant vial: 10 doses of 0.5 ml.

6.6 Special precautions for disposal and other handling

HUMENZA consists of 2 separate vials:
- One vial containing the antigen (suspension)
- One vial containing the adjuvant (emulsion)

Before use, the two components should be mixed.

Instructions for mixing the vaccine:
1. Before extemporaneous mix, the two vials (antigen and adjuvant) should be allowed to reach room temperature and must be gently swirled between hands 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), the vaccine should be discarded.
2. The vaccine is mixed by withdrawing with a sterile syringe and needle the entire content of the antigen vial and adding it into the adjuvant vial.
3. After the addition of the antigen to the adjuvant, the mixture should be gently shaken by at least 5 rotating movements. After mixing, the vaccine is a white opaque emulsion.
4. The volume of HUMENZA after mixing is at least 6 ml and allows the withdrawal of several doses (multidose vial). For the dose to be administered, see recommended posology in section 4.2.
5. After mixing HUMENZA should be stored in a refrigerator (2°C-8°C) (never place in the freezer) and should be used within 24 hours.
6. To facilitate tracking and timely disposal of partially used vials, it is suggested that the date and hour of mixing be clearly written on the label of adjuvant vial.

Instructions for the administration of the vaccine:
1. Before injection the vaccine should be allowed to reach room temperature by gently swirling the vial between hands (not more than 5 minutes).
2. Prior to each administration, the multidose vial should be gently shaken by at least 5 rotating movements.
3. The content of the multidose vial as well as the content of the syringe after withdrawal should be inspected visually. The vaccine is of a white opaque emulsion appearance. If deviations from this description and/or any foreign particulate matter are observed (including rubber particles from the stopper), the vaccine should be discarded.

4. Each vaccine dose of 0.5 ml or 0.25 ml (half-dose) is withdrawn with a new sterile syringe for injection and administered intramuscularly.

A partially used multidose vial must be discarded immediately if:
- Sterile dose withdrawal has not been fully observed.
- There is any suspicion that the partially used vial has been contaminated.
- There is visible evidence of contamination, such as change in appearance.

In order to keep the traceability of the product received by each vaccinee the name of the vaccine and the lot number should be recorded by using the stickers provided in the pack containing both the antigen and adjuvant vials.

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

7. MARKETING AUTHORISATION HOLDER

Sanofi Pasteur SA
2, avenue Pont Pasteur
F-69007 Lyon
France

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency (http://www.ema.europa.eu).