HAUTE AUTORITÉ DE SANTÉ

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TRANSPARENCY COMMITTEE

OPINION

21 September 2011

INTANZA 15 micrograms/strain, suspension for injection
B/1 0.1 ml pre-filled syringe (CIP code: 395 222-1)

Applicant: SANOFI PASTEUR MSD

influenza virus, split virion, inactivated

ATC code: J07BB02

Medicine for medical prescription only

Date of initial Marketing Authorisation: 24 February 2009 (centralised procedure) – variation: 9 June 2011

Reason for request: Inclusion on the list of medicines refundable by National Health Insurance and approved for hospitals use in populations recommended by the High Council for Public Health (2011 vaccination schedule and Opinion of 29 October 2010 concerning intradermal vaccination against influenza INTANZA 15 µg).

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Per 0.1 ml dose:

Influenza virus (split virion, inactivated) of the following strains*:

A/California/7/2009 (H1N1): derivative strain used NYMC X-179A 15 micrograms HA**

A/Perth/16/2009 (H3N2): analogue strain used NYMC X-187 derived from A/Victoria/210/2009
15 micrograms HA**
B/Brisbane/60/2008 15 micrograms HA**

* cultivated on embryonated eggs of hens from healthy flocks
** haemagglutinin

This vaccine complies with WHO (Northern Hemisphere) and with the European Union decision for the 2011/2012 season.

1.2. Background

This is the first influenza vaccine administered trough microinjection system (composed of a pre-filled syringe fitted with a 1.5 mm microneedle) enabling administration by intradermal route.

1.3. Indication

“Prevention of influenza in individuals aged 60 years and over, especially those who run an increased risk of associated complications.
The use of INTANZA should be based on official recommendations.”

1.4. Dosage

“Individuals 60-years-of-age and over: 0.1 ml.
The vaccine should be administered by intradermal route.
The recommended site of administration is the region of the deltoid.”

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2011)

J : Antiinfectives for systemic use
J07 : Vaccines
J07B : Viral vaccines
J07BB : Influenza vaccines
J07BB02 : Influenza, split virion, inactivated or surface antigen

2.2. Medicines in the same therapeutic category

2.2.1. Strictly comparator medicines

No influenza vaccine has a strictly comparable indication.

2.2.2. Not-strictly comparable medicines in the same therapeutic category

This refers to other trivalent A(H1N1), A(H3N2) and B influenza vaccines indicated in the "prevention of influenza, especially in subjects who run an increased risk of associated complications". None of these vaccines is administered by intradermal route.

AGGRIPAL, suspension for injection in a pre-filled syringe
FLUARIX, suspension for injection in a pre-filled syringe
GRIPGUARD, suspension for injection in a pre-filled syringe
IMMUGRIP, suspension for injection in a pre-filled syringe
INFLUVAC, suspension for injection in a pre-filled syringe
MUTAGRIP, suspension for injection in a pre-filled syringe
PREVIGRIP, suspension for injection in a pre-filled syringe
VAXIGRIP, suspension for injection in a pre-filled syringe

All these vaccines are indicated in a larger population (adults and children over 6 months) than that of INTANZA 15 µg except for GRIPGUARD, indicated exclusively in subjects 65 years of age and over.

2.3. Medicines with a similar therapeutic aim

TETAGRIP, suspension for injection in a pre-filled syringe indicated in adults for the combined prevention of tetanus and influenza.

3 ANALYSIS OF AVAILABLE DATA

The dossier submitted by the firm comprises in particular three comparison studies, in which the immunogenicity and safety of INTANZA 15 µg, an intradermally (ID) administered adjuvant-free vaccine, was assessed in persons aged 60 years and over.

- one phase II study (GID 16) and a phase III study (GID 17) comparing the immunogenicity of INTANZA 15 µg with that of an adjuvant-free vaccine administered by the intramuscular route (VAXIGRIP) followed up by a post-hoc analysis carried out in a sub-group of 721 persons aged over 75 years.
- a phase III study (FID01C) comparing the immunogenicity of INTANZA with that of a vaccine with adjuvant administered by the intramuscular route (GRIPGUARD).

No other specific study has been conducted in subjects aged over 75 years or having risk factors in the form of influenza-related complications.

- an exploratory and descriptive study in renal transplant patients aged from 18 to 60 years not responding to intramuscular vaccination. This study, conducted in a population aged from 18 to 60 years, given that it does not match that of the MA indication, will not be developed in this opinion.

Supplementary data:

- <u>Estimate of the impact of INTANZA 15 µg on the incidence of influenza in an epidemic period in comparison with other influenza vaccines</u>
  - A modelling of the clinical efficacy of a vaccine (establishing a correlation curve between immunogenicity and the degree of protection against infection) and a comparison of the vaccine efficacy of two vaccines administered by the intradermal route and the intramuscular route
  - A modelling of the public health impact of vaccination with INTANZA by intradermal route in comparison with influenza vaccination by the intramuscular route in terms of number of influenza cases, hospital admissions and prevented deaths.
- <u>Access to vaccine, compliance and satisfaction of vaccinated persons and prescribers as regards the technique of intradermal injection</u>
  - descriptive study assessing the acceptability to vaccinated individuals of the intradermal vaccine versus the intramuscular vaccine
  - estimation of the frequency of consultation by persons aged 60 years and over from a survey of 50 to 80-year-old patients and data from MG France based on a permanent sample of people who are socially insured by CNAMTS (National Salaried Workers' Health Insurance Fund).
  - data assessing the performance characteristics of the intradermal injection delivery system[1]
  - Australian field survey among healthcare professionals assessing satisfaction with and perception of INTANZA vaccine. This survey, whose methodology has not been developed and which is more in the nature of an opinion poll, cannot be accepted by the Committee.

[1] Laurent PE, Bonnet S, Alchas P et al. Evaluation of the clinical performance of a new intradermal vaccine administration technique and associated delivery system. Vaccine 2007; 25 (52): 8833-42

3.1. Immunogenicity

3.1.1. Study GID 16[2]

Primary objective: To demonstrate in immunogenicity terms the non-inferiority of the adjuvant-free intradermal vaccine (15 µg or 21 µg) by comparison with the 15 µg adjuvant-free vaccine administered by the intramuscular (IM) route (VAXIGRIP) in subjects aged from 60 to 85 years. In the event that non-inferiority is established, demonstrate the superiority of the ID vaccine (15 µg or 21 µg) in comparison to the 15 µg IM vaccine.

Methodology: Randomised, open-label, phase II study comparing the immunogenicity of the vaccine by the ID route with that of the adjuvant-free vaccine administered by the IM route (VAXIGRIP 15 µg) on D21 post-vaccination. Only the results relating to the 15 µg dosage of the ID vaccine will be mentioned

Primary efficacy endpoint: geometric mean of the antibody titres (GMT) for each of the three strains on D21 post-vaccination (determined by the haemagglutination inhibition technique).
Non-inferiority was established if the lower $CI_{95\%}$ limit of the ratio of the GMTs (GMT_{ID}/GMT_{IM}) was greater than 1/1.5 (≈ 0.6667) for each strain on D21 (per-protocol population).
In case non-inferiority was established, the superiority of the ID vaccine compared to the IM vaccine could be established if the lower $CI_{95\%}$ limit of the ratio (GMT_{ID}/GMT_{IM}) was greater than 1 for at least two of the three strains of vaccine (FASI[3] population).

Principal secondary endpoint:
The immunogenicity for each strain was also assessed on D21 on the basis of three immunogenicity criteria predefined by EMA[4] for the assessment of influenza vaccines:
- ration of post-vaccination/pre-vaccination MGTs (satisfied if > 2)
- seroprotection rate[5] (satisfied if > 60%)
- seroconversion rate[6] or significant increase in the levels[7] (satisfied if > 30%)

Each of the strains should meet at least one of these three immunogenicity criteria.

Results: In all, 1107 subjects aged from 60 to 85 years were included in this study and randomised into one of the three groups:
- 15 µg ID vaccine group (n = 370)
- 15 µg IM vaccine group (n = 368)
- 21 µg ID vaccine group (n = 369), whose analysis will not be described in this dossier.

Of these subjects, 1076 were included in the per-protocol population and 1100 in the FASI population. The characteristics of the subjects are presented in Table 1.

[2] Holland D, Booy R, De Looze F et al. Intradermal Influenza Vaccine Administered Using a New Microinjection System Produces Superior Immunogenicity in Elderly Adults: A Randomized Controlled Trial. J Infect Dis 2008; 198 (5): 650-8
[3] "Full analysis set for immunogenicity" population: including all the randomised subjects who have been vaccinated and who have had a post-vaccination blood sample taken.
[4] Committee for Proprietary Medicinal Products (CPMP). Note for guidance on harmonisation of requirements for influenza vaccines. CPMP/BWP/214/96. The European Agency for the Evaluation of Medicinal Products (EMA). 12 March 1997
[5] Proportion of subjects presenting an antibody titre measured by haemagglutination inhibition (IH) ≥ 40 (1/dil)
[6] Proportion of subjects presenting an antibody titre measured by HI, negative before vaccination and ≥ 40 after vaccination
[7] Proportion of subjects presenting an antibody titre measured by HI, positive before vaccination and multiplied by a factor of at least 4 after vaccination

Table 1: Characteristics of the subjects (PP population)

	15 µg ID vaccine n = 359	15 µg IM vaccine n = 358
Age (years) Mean ± standard deviation Median	 70.9 ± 6.5 69.9	 71 ± 6.6 70.8
Gender % (n) Men Women	 43.2% (155) 56.8% (204)	 47.5% (170) 62.5% (188)
Subjects at risk of 'flu-related complications* % (n)	38.7% (143)	40.8% (150)

* Subjects with at least one antecedent or a condition regarded as representing a risk factor for influenza-related complications

The immunogenicity results on the primary efficacy endpoint are presented in Table 2.

Table 2: Study GID 16: immunogenicity results on D21

	15 µg ID			15 µg IM		
Primary efficacy endpoint	Strain A(H1N1)	Strain A(H3N2)	Strain B	Strain A(H1N1)	Strain A(H3N2)	Strain B
PP population						
n	358	358	359	357	358	358
GMT ($CI_{95\%}$)	86.6 (76.5; 98.1)	402 (355; 455)	101 (90.8; 113)	57.1 (51.2; 63.7)	236 (206; 271)	67.9 (60.7; 76.0)
GMT_{ID}/GMT_{IM} ($CI_{95\%}$)	1.52 (1.29; 1.79)	1.70 (1.42; 2.05)	1.48 (1.28; 1.74)			
FASI population						
n	365	365	366	363	364	364
GMT_{ID}/GMT_{IM} ($CI_{95\%}$)	1.52 (1.29; 1.79)	1.70 (1.42; 2.04)	1.48 (1.26; 1.73)			
p	< 0.0001	< 0.0001	< 0.0001			

The non-inferiority of the 15 µg ID vaccine compared to the 15 µg IM vaccine in terms of GMT on D21 post-vaccination was established (the lower limit of the confidence interval with respect to GMT_{ID}/GMT_{IM} was greater than 1/1.5 for each of the strains).

The superiority of the 15 µg ID vaccine compared to the 15 µg IM vaccine in terms of GMT on D21 post-vaccination was established (the lower limit of the confidence interval with respect to $GMT_{\mathbf{ID}}/GMT_{IM}$ was greater than 1 for each of the strains).

Where the secondary criteria are concerned, the three assessment criteria pre-defined by EMA (ratio of post-vaccination/pre-vaccination GMTs, seroprotection rate and seroconversion rate or significant increase in the levels) were met in the INTANZA 15 µg ID group for each of the three strains.

3.1.2. Study GID 17[8]

Primary objective: Demonstrate in seroprotection terms the superiority of the 15 µg ID vaccine over the 15 µg IM vaccine.

Methodology: Randomised, open-label, phase III study comparing the immunogenicity of the 15 µg ID vaccine (INTANZA) with that of the adjuvant-free IM vaccine (VAXIGRIP15 µg) on D21 post-vaccination in subjects aged over 60 years.
The subjects were vaccinated once during three successive winter seasons. The three randomisations led to the following administration schemes:

	Vaccine administered			
Year 1 (1st randomisation)	ID (n = 2580)	IM (n = 1075)		
Year 2 (2nd randomisation)	ID (n = 2580)	ID (n = 537)	IM (n = 538)	
Year 3 (3rd randomisation)	ID (n = 2580)	ID (n = 537)	ID (n = 75)	IM (n = 75)

Primary efficacy endpoint: Geometric mean of the antibody titres (GMT) for each of the three strains on D21 after the first vaccination, determined by the haemagglutination inhibition technique (HI).
Non-inferiority was established if the lower $CI_{95\%}$ limit of the ratio of the GMTs (GMT_{ID}/GMT_{IM}) was greater than 1/1.5 for each strain (per-protocol analysis).
In the case non-inferiority was established, the superiority of the ID vaccine was assessed in terms of seroprotection (SRP) on D21 of the first vaccination. Superiority could be established if the lower $CI_{95\%}$ limit of the difference in the seroprotection rates ($SRP_{ID} – SRP_{IM}$) on D21 was greater than 0 for at least two of the three vaccine strains (FASI analysis).

Principal secondary endpoints:
- immunogenicity criteria pre-defined by EMA on D21 of the first vaccination
- persistence of antibodies at 3, 6 and 12 months after the first injection.
- immunogenicity criteria on D21 of the second and third annual vaccinations

Results: In all, 3707 subjects aged over 60 years were included and randomised into one of the two groups for the first vaccination: 15 µg ID group, n = 2618 and 15 µg IM group, n = 1089. Of these subjects, 3626 were included in the per-protocol population and 3685 in the FASI population. The characteristics of the subjects are presented in Table 3.

Table 3: Characteristics of the subjects (FASI population)

	15 µg ID vaccine n = 2604	15 µg IM vaccine n = 1081
Age (years) Mean ± standard deviation ≥ 70 (n, %)	 70.7 ± 6.8 1349 (51.8)	 70.9 ± 6.7 551 (51.0)
Gender % (n) Men Women	 45.5% (1186) 54.5% (1418)	 45.8% (495) 54.2% (586)
Subjects with increased risk of 'flu-related complications* % (n)	65.6% (1708)	63.6% (687)

* Subjects with at least one antecedent or a condition regarded as representing a risk factor for influenza-related complications

[8] Arnou R, Icardi G, De Decker M et al. Intradermal influenza vaccine for older adults: A randomized controlled multicenter phase III study. Vaccine 2009; 27: 7304-12

After the first vaccination, the three assessment criteria pre-defined by EMA, ratio of post-vaccination/pre-vaccination GMTs, seroprotection rates and seroconversion rates or significant increase in the levels, were met in the INTANZA 15 µg ID group for the two strains A(H1N1) and A(H3N2). With the B strain, of the three criteria pre-defined by EMA, the seroprotection criterion was not met in the two groups.

The immunogenicity results on the primary efficacy endpoint are presented in Table 4.

Table 4: Study GID 17: immunogenicity results on D21 (first vaccination)

	15 µg ID			15 µg IM		
Primary efficacy endpoint	Strain A(H1N1)	Strain A(H3N2)	Strain B	Strain A(H1N1)	Strain A(H3N2)	Strain B
PP population						
n	2549	2549	2546	1064	1065	1065
GMT ($CI_{95\%}$)	81.9 (78.1; 85.8)	297 (281; 314)	39.9 (38.3; 41.7)	68.8 (63.8; 74.2)	181 (166; 197)	34.8 (32.5; 37.2)
GMT_{ID}/GMT_{IM} ($CI_{95\%}$)	1.190 (1.091; 1.300)	1.641 (1.483; 1.816)	1.148 (1.062; 1.242)			
FASI population						
n	2595	2595	2592	1077	1078	1078
GMT ($CI_{95\%}$)	81.9 (78.2; 85.8)	298 (282; 315)	39.9 (38.2; 41.6)	69.1 (64.1; 74.4)	181 (167; 197)	34.9 (32.7; 37.3)
Seroprotection rate (%)	77.0	93.3	55.7	71.2	87.8	49.1
$SRP*_{ID}$-SRP_{IM} ($CI_{95\%}$) of the difference	5.78 (2.88; 8.51)	5.49 (3.40; 7.76)	6.60 (3.05; 10.13)			
p	<0.0001	<0.0001	<0.0001			

*SRP = seroprotection

The non-inferiority of the 15 µg ID vaccine compared to the 15 µg IM vaccine in terms of GMT on D21 was established (the lower limit of the confidence interval of the ratio of the GMTs was greater than 1/1.5 for each of the strains in the PP population).
The superiority of the 15 µg ID vaccine compared to the 15 µg IM vaccine in terms of seroprotection on D21 was established (the lower limit of the confidence interval of the difference (SRP_{ID} – SRP_{IM}) was greater than 0 for each of the strains in the FASI population).

The immunogenicity data at 3, 6 and 12 months after the first injection and those on D21 of the second and third vaccinations have only been the subject of a descriptive analysis.
In terms of the persistence of antibodies after the first injection, the seroprotection levels decrease gradually up to 12 months (M12) for the three strains, regardless of the route of administration. At 3 (M3) and 6 months (M6), the seroprotection rates remained above 60% (EMA criterion) in the 15 µg ID and 15 µg IM groups for the strains A(H1N1) and A(H3N2), except for the A(H1N1) strain at M6 in the IM group. At M12, the percentages of seroprotection remained above 60% for the A(H3N2) strain in both groups, but not for strains A(H1N1) and B. For the strains A(H1N1) and A(H3N2), the percentage of seroprotection at M6 and M12 was higher in the group of subjects vaccinated by the ID route than that of the IM group. For the B strain, the percentage of seroprotection at M6 and M12 was lower in the group vaccinated by the ID route than that vaccinated by the IM route.
The results on D21 of the second and third vaccination by the ID route suggest that the immune response in terms of seroprotection is not diminished by revaccination.

A post-hoc analysis not envisaged by the protocol was carried out in a sub-group of 721 persons aged over 75 years.
The analysis focused on the OIAS (Other Immunogenicity Analysis Set) population during the first vaccination year. The immunogenicity data on Day 21 were analysed.
The pre-vaccination antibodies were comparable in the intramuscular and intradermal vaccine groups for each of the three strains as regards the geometric means of the titres (GMT) and the level of seroprotection.

Summary: Immunogenicity criteria pre-defined by EMA
For each strain the recommendations are to meet at least one of the 3 criteria:
- ratio of post-vaccination/pre-vaccination GMTs (satisfied if > 2)
- seroprotection rate[9] (satisfied if > 60%)
- seroconversion rate[10] or significant increase in the antibody titres[11] (satisfied if > 30%)

Results: The GMT ratio and the seroprotection rate were achieved for each of the three strains in persons aged 75 and over.
The seroconversion rate or significant increase in the antibody titres was achieved for the H3N2 strain and the B strain.
However, the immunogenicity data on D21 emanating from an exploratory analysis do not support the conclusion that the intradermal route is superior to the intramuscular route in over-75-year-olds. Indeed, the differences observed favour the intradermal route for two of the three strains (H1N1 and H3N2) in terms of the GMT ratio, only for the H3N2 strain in terms of the seroconversion rate or significant increase in the antibody titres and only for the B strain in terms of the seroprotection rate.

3.1.3. Study FID01C[12]

Primary objective: Demonstrate the non-inferiority in terms of immunogenicity of the 15 µg vaccine by the ID route in comparison to the 15 µg vaccine by the IM route with adjuvant (in subjects aged 65 years and over). In case of non-inferiority, demonstrate the superiority of the 15 µg ID vaccine in comparison to the 15 µg vaccine with adjuvant administered by the intramuscular route.

Methodology: Randomised, open-label, phase III study comparing the immunogenicity of the 15 µg ID vaccine (INTANZA) with that of a 15 µg IM vaccine with adjuvant (GRIPGUARD).

Primary efficacy endpoint: GMT for each of the three strains on D21 after vaccination, determined by the HI technique.
Non-inferiority was established if the upper $CI_{95\%}$ limit of the ratio of the geometric means of the titres GMT_{IM}/GMT_{ID} was below 1.5 for the three strains (PP population analysis).
In case of non-inferiority, the superiority of the ID vaccine over the IM vaccine with adjuvant could be established if the upper $CI_{95\%}$ limit of the ratio GMT_{IM}/GMT_{ID} was less than 1 for at least two of the three vaccine strains (FASI population analysis).

Principal secondary endpoint: GMT for each of the three strains on D21, determined by the SRH technique (Single Radial Haemolysis). The non-inferiority and superiority hypotheses were the same as for the primary criterion.

[9] Proportion of subjects presenting an antibody titre measured by haemagglutination inhibition (HI) ≥ 40 (1/dil)
[10] Proportion of subjects presenting an antibody titre measured by HI negative before vaccination and ≥ 40 after vaccination
[11] Proportion of subjects presenting an antibody titre measured by HI, positive before vaccination and multiplied by a factor of at least 4 after vaccination
[12] Van Damme P, Arnou R, Kafeja F et al. Evaluation of non-inferiority of intradermal versus adjuvanted seasonal influenza vaccine using two serological techniques: a randomised comparative study. BMC Infectious Diseases 2010; 10: 134

Results: In all, 795 subjects were included in the study, 398 in the 15 µg ID vaccine group and 397 in the 15 µg IM vaccine group. Of these subjects, 775 were selected in the per-protocol population. The patients characteristics are presented in Table 5.

Table 5: Characteristics of the subjects (per-protocol population)

	15 µg ID vaccine n = 390	15 µg IM vaccine with adjuvant n = 385
Age (years) Mean ± standard deviation Median ≥ 75 years (n, %)	 73.9 ± 6,3 72.6 148 (37.9)	 74.7 ± 6,6 74.0 171 (44.4)
Gender % (n) Men Women	 48.2% (188) 51.8% (202)	 44.7% (172) 55.3% (213)
Subjects at risk of 'flu-related complications* % (n)	54.3% (216)	51.1% (203)

* Subjects with at least one antecedent or a condition regarded as representing a risk factor for influenza-related complications

The immunogenicity results on the primary assessment criterion are presented in Table 6.

Table 6: Study FID01C: immunogenicity results on D21 assessed by the HI method (PP analysis)

	15 µg ID vaccine n = 398			15 µg IM vaccine n = 397		
Primary efficacy endpoint*:	Strain A(H1N1)	Strain A(H3N2)	Strain B	Strain A(H1N1)	Strain A(H3N2)	Strain B
GMT ($CI_{95\%}$)	108.3 (95.4; 123)	259.9 (233.5; 289.3)	36.9 (33.6; 40.5)	122.1 (109.1; 136.7)	341.4 (306.7; 380.1)	39.9 (33.6; 43.8)
GMT_{IM}/GMT_{ID} ($CI_{95\%}$)	1.13 (0.95; 1.34)	1.31 (1.13; 1.53)	1.08 (0.95; 1.23)			

The non-inferiority of the INTANZA vaccine compared to the vaccine administered by the intramuscular route with adjuvant was demonstrated for two of the three strains (A(H1N1) and B) in immunogenicity terms by the haemagglutination inhibition method (the upper limit of the confidence interval of the ratio of the GMTs was less than 1.5 for these two strains).
As the non-inferiority of the 15 µg ID vaccine was not demonstrated for the three strains, its superiority compared to the IM vaccine with adjuvant was not assessed.

By the SRH method, the non-inferiority of the 15 µg ID vaccine compared to the 15 µg IM vaccine with adjuvant was established in terms of the GMT on D21 for the three vaccine strains (PP population). The upper limit of the confidence interval for the ratio of the GMTs was less than 1.5 for the three strains (1.34 for the A(H1N1) strain, 1.34 for the A(H3N2) strain and 1.17 for the B strain).

3.1.4. Other data

➢ Impact of INTANZA on the incidence of influenza in an epidemic period:

- modelling of the clinical efficacy of a vaccine (establishing a correlation curve between immunogenicity and the degree of protection against infection) and a comparison of the vaccine efficacy of two influenza vaccines administered by the intradermal route and the intramuscular route

The authors proceeded in two stages:

1 – Modelling of vaccine efficacy in order to establish the vaccine protection probability curve as a function of antibody levels:

In the absence of any study assessing the clinical efficacy of the vaccine INTANZA 15 µg in terms of a reduction in influenza cases, a mathematical model was initially developed to establish the relationship between antibody titres measured by the haemagglutination inhibition (HI) method and protection against infection.[13]
The authors used a Bayesian approach based on a Markov Chain Monte Carlo Model.
The model was constructed on the basis of studies available in the literature from 1945 to 2006 from which were extracted immunogenicity data and information about possible cases of influenza. Of the 36 publications identified, 15 were used for constructing the correlation curve between the levels of HI antibodies and the degree of vaccine protection: six comparison studies, five clinical trials (with biological confirmation of the diagnosis by serology or virus isolation) and four cohort studies. It should be pointed out that only one of these studies included patients aged over 60 years. These fifteen studies covered 5889 observations and 1304 cases of influenza.
The use of this curve could help to predict the efficacy of influenza vaccines as a function of the immunogenicity data and to compare the various vaccines.

2 – Comparison of the vaccine protection of two influenza vaccines administered either by the intradermal route or by the intramuscular route

In a second stage, a comparison of the clinical vaccine efficacy, as predicted from the mathematical model developed, of the two vaccines administered by the intradermal route and the intramuscular route was made according to the pooled immunogenicity results taken from the two clinical studies GID 16 and GID 17, which compared the two routes of administration over three consecutive years.[14]
The vaccine protection predicted on the basis of the model was 63.3% for the intradermal route and 54.4% for the intramuscular route, i.e. an increase in absolute vaccine efficacy of 9.0% [7.3-10.6] and relative efficacy of 16.5% [12.7-20.1] (difference in vaccine efficacy between the two routes of administration/vaccine efficacy of the IM route).

This model constitutes an interesting approach; however, its reliability is debatable, given the limitations inherent in the quality of the data used. Indeed, the model relies on aggregated data and would have been interesting to have individual data to be able to judge the influence of interindividual variability on the results. Information about factors potentially causing confusion is limited (pre-vaccination antibody titres, influenza vaccination history, prevalence of comorbidities).

[13] Coudeville L, Bailleux F, Riche B et al. Relationship between haemagglutination-inhibiting antibody titres and clinical protection against influenza: development and application of a Bayesian random-effects model. BMC Med Res Methodol 2010; 10 (18): 3-11
[14] Coudeville L, André P, Bailleux F et al. A new approach to estimate vaccine efficacy based on immunogenicity data applied to influenza vaccines administered by the intradermal or intramuscular routes. Human Vaccine 2010; 6(10): 841-848

Moreover, the data used were published over several years, the studies taken into account were performed using different methodologies and relate to heterogeneous populations that included few patients over the age of 65 years.

- modelling estimating the public health impact of vaccination with INTANZA by the intradermal route compared to vaccination by the intramuscular route

An assessment of the public health impact of the complete substitution of vaccination with INTANZA by other influenza vaccines was carried out in order to estimate the number of influenza cases, hospital admissions and prevented deaths in France.
An analytical decision model, initially developed to compare two vaccination strategies[15] in subjects over the age of 50 years, was used and adapted to the French situation.
The parameters adopted for the demographic parameters were taken from the data established by INSEE (French National Institute of Statistics and Economic Studies), those for the epidemiological parameters from the data established by the network of influenza observation groups (influenza attack rate in the over 65s), by PMSI (programme for clinical information systems) (influenza hospitals) and by the epidemiological centre on the medical causes of death (deaths attributable to influenza), and those for the vaccination parameters from the data established by Health Monitoring and Health Insurance Institute (vaccination coverage observed in 2009/2010). The vaccination efficacy data were estimated on the basis of observational studies in elderly persons living at home or in an institution.

The public health impact of vaccination with INTANZA 15 µg in France was studied in two groups of persons concerned with the recommendations for influenza vaccination: persons aged 65 and over and patients aged from 60 to 64 years with a chronic condition.

Results:
In patients 65 years old and over, the model predicts a variation of 35,156 to 39,215 influenza episodes a year, of 506 to 565 hospital admissions a year and of 501 to 559 deaths a year.

In patients aged from 60 to 64 years with a chronic condition, the model predicts a variation of 1382 to 1829 influenza episodes a year, of 20 to 26 hospital admissions a year and of 20 to 26 deaths a year.

Due to the strong and unrealistic hypothesis of the total substitution of the INTANZA vaccine for the other influenza vaccines, the results of the modelling of the public health impact at 5 years of using INTANZA in France cannot be taken into account. Besides, the estimates of the parameters of the model selected are scarcely justifiable and the results of the sensitivity analyses not provided.

- Access to the vaccine, compliance and satisfaction of vaccinated persons and prescribers as regards the technique of intradermal injection

- descriptive study assessing the acceptability to vaccinated individuals of the intradermal vaccine versus the intramuscular vaccine

15 Aballéa S, Chancellor J, Martin M, Wutzler P, Carrat F, Gasparini R, Toniolo-Neto J, Drummond M, Weinstein M. The cost-effectiveness of Influenza vaccination for people aged to 50 to 64 years: an international Model. Value Health. 2007 Mar-Apr; 10 (2): 98-116.

A descriptive study was published,[16] assessing the acceptability of the influenza vaccine by the intradermal and intramuscular routes. This study was conducted in 5305 adults, including 3407 aged over 60 years, in the form of a self-assessment (VAPI[17] Questionnaire). Local reactions to the vaccine were "totally acceptable" or "very acceptable" for over 96% of the vaccinated subjects in the two groups. The percentage of subjects wishing to be vaccinated the following year by the same method of injection was the same by the IM or ID route (89%).

- A SYNOVATE quantitative survey (January 2007) analysed the frequency with which patients visited their doctor's surgery: from the age of 65 years, 87% of patients consulted their doctor at least once every 2 to 3 months

- the MG France data emerging from the permanent sample of CNAM TS socially insured individuals indicate that in 2003 no fewer than 9 out of 10 active pensioners consulted their GPs every 2 months. From the age of 75, more than 9 out of 10 pensioners consulted their GPs 11 times a year.

The mandatory medical prescription required with INTANZA vaccine does not appear, therefore, to curb access to the vaccine.

- data assessing the characteristics of the performance of the intradermal delivery system[18]

The performance of the microneedle intradermal injection system was assessed on the basis of two clinical studies in 645 adults aged from 18 to 80 years.
The first study involved 168 general practitioners at six French research sites. The second involved 15 nurses practising at a single research site. Practitioners were divided into several groups each receiving different levels of training in the use of the intradermal injection system.
The primary endpoint was reproducibility of the volume injected. The other endpoints were assessment of the tolerability and perception of the feasibility of the injection by the doctors and nurses.
The success rate of the injection (residual volume of liquid on the skin surface less than 10 µl) was high (> 95%) irrespective of the level of training that the health professionals received.
The best success rate was found in the group of researchers who had received no additional information or training in the injection device.
The data on the feasibility of the intradermal technique are reassuring but remain to be confirmed in everyday medical practice.

3.2. Adverse effects (extract from the SPC)

"During the course of three randomised, open-label clinical trials, safety was assessed in 3372 patients receiving an injection of INTANZA.
The safety assessment was performed in all the subjects during the first 3 weeks after vaccination and the serious adverse reactions were recorded during a 6-month follow-up period in 2974 subjects (population of two of the three clinical studies).
The most frequent reactions occurring after administration of the vaccine were local reactions at the injection site".

[16] Reygrobellet C, Viala-Danten M, Meunier J, Werber F, Nguyen VH. Perception and acceptance of intradermal influenza vaccination: patient reported outcomes from phase 3 clinical trial. Hum Vaccin, 2010, Apr 26, 6(4)
[17] Chevat C, Viala-Danten M, Dias-Barbosa C, Nguyen VH. Development and psychometric validation of a self-administered questionnaire assessing the acceptance of influenza vaccination: the vaccinees perception of injection (VAPI) questionnaire. Health and Quality of Life Outcomes, 2009, 7, 1-10
[18] Laurent PE, Bonnet S, Alchas P et al. Evaluation of the clinical performance of a new intradermal vaccine administration technique and associated delivery system. Vaccine 2007;25(52):8833-42

The most frequently reported adverse effects were the following:
Very common (frequency ≥1/10):
- local reactions: redness, induration, swelling, pruritus, pain,
- headache,
- myalgia.

Common (frequency ≥1/100 to <1/10):
- faintness, shivering, fever,
- local reactions: bruising.

“Local reactions apparent after intradermal administration were more common than after intramuscular administration of a comparison vaccine with or without adjuvant. Most reactions disappeared spontaneously within 1 to 3 days of their appearance.
The systemic tolerability profile of INTANZA is similar to that of a comparison vaccine, with or without adjuvant, administered by the intramuscular route.”

3.3. Conclusion

The studies GID 16 and GID 17, conducted in subjects aged over 60 years (average age 71 years) showed that for each of the three vaccine strains the immunogenicity obtained with INTANZA 15 µg was superior to that obtained with an adjuvant-free vaccine administered by the intramuscular route (VAXIGRIP 15 µg).

In a third study (study FID01C) carried out in subjects aged over 65 years (average age 74 years):
- the non-inferiority of the INTANZA vaccine in relation to the vaccine with adjuvant by the intramuscular route (GRIPGUARD) was shown for two out of three strains in terms of immunogenicity by the haemagglutination inhibition method. The primary efficacy endpoint for this study was therefore not attained.

No specific study was carried out in subjects aged over 75 years or having risk factors in the form of influenza-related complications.
A post-hoc analysis of the study GID 17 (not envisaged by the protocol) was performed in a sub-group of 721 persons aged over 75 years and this does not support the conclusion that the intradermal route is superior to the intramuscular route in over-75-year-olds.

Besides, no study of protective efficacy has been conducted.

The frequency of local reactions was greater with INTANZA 15 µg than with the comparison vaccines administered by the intramuscular route with or without adjuvant. The systemic safety profile of INTANZA is similar to that of the comparison vaccine, with or without adjuvant, administered by the intramuscular route.

Modelling of the clinical efficacy of a vaccine as a function of the antibody titres constitutes an interesting approach; however, its reliability is debatable, given the limitations inherent in the quality of the data used.
The results of the modelling of the public health impact at 5 years of using INTANZA in France cannot be taken into account in view of the unrealistic nature of the assumptions adopted (total substitution with INTANZA of all other influenza vaccines).

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Influenza is a highly contagious, acute viral disease. Complications, sometimes serious, can occur in elderly or frail patients.

This proprietary medicinal product falls into the category of a preventive treatment.

The efficacy (immunogenicity)/adverse effects ratio is high.

Public health benefit

Influenza is a common contagious disease that can be serious for certain categories of patients (comorbidities and/or age over 65 years, in particular). It constitutes a moderate public health burden.

Reducing the morbidity and mortality levels during influenza epidemics does constitute a public health need. Improving the level of seasonal influenza vaccine coverage is one of the priorities determined by the Law of 9 August 2004 in relation to public health (objective 39: target of a minimum vaccine coverage of 75%). As this target has not been met, the need is still there.

The available data for the proprietary medicinal product INTANZA are based on immunogenicity data obtained in populations aged predominantly from 60 to 85 years, as well as on data on the acceptability of various routes of injection.

It is not possible to presume on the basis of these data that this vaccine offers anything additional in terms of morbidity/mortality or the rate of vaccine coverage relative to other influenza vaccines that are currently refundable.

The transferability of the results of studies to clinical practice is not assured:

- firstly, in the absence of any studies in populations at risk from influenza-related complications targeted by current recommendations, especially in at-risk populations whose immune response is impaired and/or likely to benefit from the intradermal route (immunosuppressed patients, patients over the age of 85 years, patients on anticoagulants, etc.)

- secondly, because it depends on the correct implementation of the intradermal injection technique.

Moreover, the public health impact remains dependent on the reach of a sufficient level of vaccine coverage in the recommended population, and given that access to this vaccine requires a medical prescription, this will not be so simple.

Consequently, the response to the identified public health need likely to be offered by the proprietary medicinal product INTANZA is not assessable at this stage.

Therefore, in the light of present knowledge, the public health benefit of the proprietary medicinal product INTANZA is not quantifiable.

- Vaccination alternatives refundable by National Insurance do exist.

Influenza vaccines have an important role in the strategy for preventing influenza and its complications.

The actual benefit of INTANZA 15 µg is substantial in populations aged over 60 years and recommended by the High Council for Public Health (HCSP).

4.2. Improvement in actual benefit

In light of the available data, the Transparency Committee considers that the vaccine INTANZA 15 µg, administered by the intradermal route, offers no improvement in actual benefit (IAB V) as regards the prevention of influenza in populations over the age of 60 years and recommended by the High Council for Public Health.

The Committee notes that this method of administration by the intradermal route is potentially more immunogenic, but its impact on the effects of influenza has not been demonstrated.

4.3. Therapeutic use

4.3.1 According to the guidelines in the 2011 vaccination schedule [19]

Persons eligible for vaccination with INTANZA against seasonal influenza are the following:

- Persons aged 65 years and over.
- Persons aged between 60 and 64 years with the following conditions:
  - Chronic bronchopulmonary conditions meeting the criteria of chronic condition 14 (according to the French classification of chronic conditions)
  - Chronic obstructive or restrictive respiratory failure of whatever cause, including neuromuscular disease at risk of respiratory decompensation, malformation of the upper or lower airways, pulmonary malformations or malformations of the rib cage
  - Chronic respiratory diseases not satisfying the criteria of the chronic condition but likely to be exacerbated or decompensated by an influenza-like illness, including asthma, chronic bronchitis, bronchiectasis, bronchial hyperactivity
  - Bronchopulmonary dysplasia[20]
  - Cystic fibrosis
  - Cyanotic congenital heart disease or with PAH and/or heart failure
  - Severe heart failure
  - Severe valve disease
  - Severe arrhythmia justifying long-term treatment
  - Coronary artery disease
  - History of stroke
  - Severe forms of neurological and muscular conditions (including myopathy, poliomyelitis, myasthenia, Charcot's disease)
  - Paraplegia and tetraplegia with diaphragmatic disorder
  - Severe chronic kidney disease
  - Nephrotic syndromes
  - Drepanocytosis, homozygotes and double heterozygotes S/C, thalassodrepanocytosis
  - Diabetes type 1 and 2
  - Primitive or acquired immunodeficiency (cancer and blood diseases, organ and haematopoietic stem-cell transplantation, hereditary immune deficiency, inflammatory and/or autoimmune diseases receiving immunosuppressive treatment), except persons receiving regular immunoglobulin therapy. HIV-infected subjects regardless of age and immune and virological status.

- Family members of infants aged less than 6 months presenting severe influenza risk factors defined as follows: premature, in particular those suffering from bronchial

[19] 2011 vaccination schedule
[20] Treated during the course of the previous six months by mechanical ventilation and/or prolonged oxygen therapy and/or continuous medicinal treatment (corticosteroids, bronchodilators, diuretics).

dysplasia-type after effects and children with congenital heart disease, congenital immune deficit, pulmonary, neurological or neuromuscular disease or a long-term illness.

- Persons staying in a convalescent home or in a social healthcare home, regardless of age.
- In a professional environment:
  - Health professionals and any professional in regular and prolonged contact with subjects at risk from severe influenza;
  - Cruise-ship and airplane personnel and healthcare personnel

The Committee draws attention to the fact that healthcare professionals (except those in private practice or working for themselves) and other professionals in regular and prolonged contact with persons at risk from severe influenza may be covered by their employer according to Article R4426-6 of the Labour Code: “at the proposal of the occupational health practitioner, the employer recommends that all employees who have not been immunised against pathogenic biological agents to which they are or could be exposed should arrange for appropriate vaccinations at their own expense”.

For the 2011-2012 influenza season, the HCSP recommended in its opinion of 13 July 2011 that obese persons (those with a body mass index equal to or greater than 30) should also be vaccinated against seasonal influenza.

4.3.2 Place of INTANZA 15 µg in the prevention strategy against seasonal influenza

The transparency Committee considers that INTANZA 15 µg can be used in subjects aged 60 years and over as covered by the recommendations in the 2011 vaccination schedule. It does not advise its use in preference to other influenza vaccines.

4.4. Target population (except for professionals)

The target population of INTANZA 15 µg is represented by adults over the age of 60 years as per the recommendations on vaccination against seasonal influenza given in the 2011 Vaccination Schedule.

The population eligible for vaccination with INTANZA vaccine against seasonal influenza is estimated quantitatively on the basis of the following statistics:
- there are 10.9 million persons aged 65 years or over;[21]
- about 955,000 persons aged from 60 to 64 years have risk factors for complications associated with seasonal influenza

(see Appendix 2);

The population eligible for vaccination against seasonal influenza with INTANZA vaccine is estimated to be around 11.9 million persons (excluding populations recommended in a professional capacity).

[21] INSEE data as of 1 January 2011

4.5. Transparency Committee recommendations

The transparency Committee recommends inclusion in the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use and various public services in the indication and at the dosage in the Marketing Authorisation and in the populations for whom vaccination is recommended in the current vaccination schedule.

The transparency Committee requests that the company provides data allowing it to:
- describe the characteristics of the population receiving the INTANZA vaccine,
- assess compliance and prescriber satisfaction with regard to the vaccine and with the practical implementation of the intradermal injection technique;
- confirm the immunogenicity conferred by the vaccine in actual practice in the target groups concerned, allowing in particular an estimation of its impact on the incidence of influenza (in an epidemic period) in comparison with other vaccines, including in at-risk populations likely to benefit from it (immunosuppressed subjects, those over the age of 85 years, subjects on anticoagulants, etc.).

Packaging: appropriate for the prescription conditions

Reimbursement rate: 65%

APPENDIX 1

REASONS FOR REQUESTING A POST-MARKETING STUDY

INTANZA (influenza vaccine used by intradermal injection)

For the INTANZA dossier (influenza vaccine used by intradermal injection) indicated in the prevention of influenza in individuals aged 60 years and over, in particular in those with a high risk of associated complications, the ISPEP Group (Public health benefit and post-registration studies) has assessed the public health benefit expected from this proprietary medicinal product and has recommended to the Transparency Committee that it should request the company to provide supplementary information about this vaccine.

This request for supplementary data is justified on the basis of the following principal elements:

- The best potential immunogenicity conferred by this vaccine remains to be confirmed in at-risk populations whose immune response is altered and/or likely to benefit from the intradermal route (immunosuppressed patients, patients over the age of 85 years, patients on anticoagulants, etc.); indeed the immunogenicity data relating to the population of patients over the age of 75 years and coming from an exploratory analysis of the study GID 17 (not envisaged by the protocol) do not support the conclusion that the intradermal route is superior to the intramuscular route in those over 75 years of age.
- The latter will depend on carrying out the injection technique using the intradermal route correctly in everyday practice and on professionals using the injection device properly;
- Demonstrating that this method offers better protection against influenza in comparison to the adjuvant-free vaccine relies only on these immunological criteria and not on public health criteria (morbid events prevented).
  Modelling the clinical efficacy of a vaccine as a function of the antibody titres, while constituting an interesting approach, has not been judged satisfactory in view of the limitations inherent in the quality of the data used. The results of modelling the public health impact at 5 years of using INTANZA in France could not be taken into account in view of the unrealistic nature of the assumptions adopted (total substitution with INTANZA of all other influenza vaccines).

Such data would make it possible to determine whether in actual conditions of use, INTANZA offers greater protection against influenza in these at-risk populations and whether it can offer a benefit in morbidity terms by comparison with the other available alternatives.

In addition, the Committee has responded favourably and has taken on board the working group recommendations.

Quantitative estimate of the target population for the influenza vaccines (excluding the professional environment)

Appendix 2

HCSP recommendations regarding vaccination against seasonal influenza (opinion of 17/12/10), for the 2011 vaccination schedule	**Quantitative estimate**[‡]	**n**
1. <u>Persons aged 65 years and over</u>:	According to INSEE data,[33] the number of persons aged 65 years and over in France is estimated at 10,896,697 as at 01/01/2011.	10.9 million
2. <u>Persons, including children aged 6 months and older and pregnant women suffering from the following conditions</u>:		
• **Chronic bronchopulmonary conditions meeting the criteria of chronic condition 14 (according to the French classification of chronic conditions) – asthma and COPD**	According to data from the French general health insurance scheme for 2009, the number of persons aged from 60 to 64 years qualifying for reimbursement of costs on the grounds of chronic condition 14 was 33,776 or, extrapolated to the French population, approximately 40,000 persons.	40,000
• **Chronic obstructive or restrictive respiratory failure of whatever cause, including neuromuscular disease at risk of respiratory decompensation, malformation of the upper or lower airways, pulmonary malformations or malformations of the rib cage**	This population is not quantifiable. However, this population may be regarded as being in large part represented by patients suffering from "severe forms of neurological and muscular conditions" (chronic condition 9) and patients suffering from "severe chronic respiratory failure" (chronic condition 14).	--
• **Chronic respiratory diseases not satisfying the criteria of the chronic condition but likely to be exacerbated or decompensated by an influenza-like illness, including asthma, chronic bronchitis, bronchiectasis, bronchial hyperreactivity**	Data from the 10-yearly health survey INSEE 2003[22] put the estimate for the prevalence of chronic bronchitis at 3.5% in the population aged 45 years and over, or about 141,000 persons aged from 60 to 64 years.[23] The current prevalence of asthma[24] is estimated at nearly 7% among adults aged 60 years and over, or around 283,000 persons aged from 60 to 64 years. Excluding patients with chronic conditions, this population is estimated at around 384,000 persons.	384,000
• **Bronchopulmonary dysplasia *(treated during the course of the previous six months by mechanical ventilation and/ or prolonged oxygen therapy and/or continuous medicinal treatment (corti-costeroids, bronchodilators, diuretics).***	This population is not quantifiable. It should relate to only a small number of persons compared to other recommended populations.	--
• **Cystic fibrosis**	According to data from the French general health insurance scheme for 2009, the number of persons aged from 60 to 64 years	50

22 Fuhrman et al. Bronchite chronique : prévalence et impact sur la vie quotidienne. Analyse des données de l'enquête santé Insee 2002-2003 (www.invs.sante.fr)

23 Estimate of the population aged from 60 to 64 years: 4,037,451 (www.insee.fr)

24 Asthma attacks in the last 12 months or current asthma treatment

	qualifying for reimbursement of costs on the grounds of chronic condition 18 “cystic fibrosis” was 41 or, extrapolated to the French population, approximately 50 persons.	
• **Cyanotic congenital heart disease or with PAH and/or heart failure** • **Severe heart failure** • **Severe valve disease** • **Severe arrhythmia justifying long-term treatment**	According to data from the French general health insurance scheme for 2009, the number of persons aged from 60 to 64 years qualifying for reimbursement of costs on the grounds of chronic condition 5 “severe heart failure, severe arrhythmia, severe heart valve disease, severe congenital heart disease” was 51,896 or, extrapolated to the French population, approximately 62,000 persons.	62,000
• **Coronary artery disease**	According to data from the French general health insurance scheme for 2009, the number of persons aged from 60 to 64 years qualifying for reimbursement of costs on the grounds of chronic condition 13 “Coronary artery disease” was 106,574 or, extrapolated to the French population, approximately 127,000 persons.	127,000
• **History of stroke**	According to data from the French general health insurance scheme for 2009, the number of persons aged from 60 to 64 years qualifying for reimbursement of costs on the grounds of chronic condition 1 “Disabling stroke” was 26,592 or, extrapolated to the French population, approximately 32,000 persons.	32,000
• **Severe forms of neurological and muscular conditions (including myopathy, poliomyelitis, myasthenia, Charcot’s disease)**	According to data from the French general health insurance scheme for 2009, the number of persons aged from 60 to 64 years qualifying for reimbursement of costs on the grounds of chronic condition 9 “Severe form of neurological and muscular disorders, severe epilepsy” was 14,841 or, extrapolated to the French population, approximately 18,000 persons.	18,000
• **Paraplegia and tetraplegia with diaphragmatic disorder**	According to data from the French general health insurance scheme for 2009, the number of persons aged from 60 to 64 years qualifying for reimbursement of costs on the grounds of chronic condition 20 “Paraplegia” was 2514 or, extrapolated to the French population, approximately 3000 persons.	3,000
• **Severe chronic kidney disease** • **Nephrotic syndromes**	According to data from the French general health insurance scheme for 2009, the number of persons aged from 60 to 64 years qualifying for reimbursement of costs on the grounds of chronic condition 19 “Chronic kidney disease and nephrotic syndrome” was 8614 or, extrapolated to the French population, approximately 10,000 persons.	10,000
• **Drepanocytosis, homozygotes and double heterozygotes S/C, thalassodrepanocytosis**	This population is not quantifiable. It should relate to only a small number of persons compared to other recommended populations.	--
• **Type 1 and 2 diabetes**	According to data from the French general health insurance scheme for 2009, the number of persons aged from 60 to 64 years	316,000

	qualifying for reimbursement of costs on the grounds of chronic condition 8 "Type 1 diabetes and type 2 diabetes" was 265,442 or, extrapolated to the French population, approximately 316,000 persons.	
• **Primitive or acquired immuno-deficiency (cancer and blood diseases, organ and haematopoietic stem-cell transplantation, hereditary immune deficiency, inflammatory and/or autoimmune diseases receiving immunosuppressive treat-ment), except persons receiving regular immunoglobulin therapy. HIV-infected subjects regardless of age and immune and virological status.**	According to data from the French general health insurance scheme for 2009, the number of persons aged from 60 to 64 years qualifying for reimbursement of costs on the grounds of at least one of the following chronic conditions (chronic condition 30: Malignant tumours, chronic condition 7: Severe primitive immune deficit necessitating prolonged treatment, infection by human immunodeficiency virus; chronic condition 28: Sequelae of organ transplantation, chronic condition 21: Polyarteritis nodosa, acute disseminated lupus erythematosus, generalised scleroderma, chronic condition 25: Multiple sclerosis, chronic condition 22: Rheumatoid polyarthritis, chronic condition 24: Evolving ulcerative colitis and Crohn's disease, chronic condition 27: Ankylosing spondylitis) was estimated at 291,963 or, extrapolated to the French population, 348,000 persons. Of those with acquired immunodeficiency syndrome, the proportion receiving immunosuppressive treatment is unknown.	348,000
Total of the populations suffering from a disease that makes them eligible for vaccination against seasonal influenza	According to data from the French general health insurance scheme for 2009, 802,212 persons aged from 60 to 64 years have been identified with at least one of the chronic conditions corresponding to a disease mentioned in the recommendations for vaccination against seasonal influenza. Extrapolating these data to the French population it is possible to estimate this population at 955,000 persons. To this population should be added the approximately 384,000 persons with chronic bronchitis.	Around 955,000
3. <u>Family members of infants aged less than 6 months presenting severe influenza risk factors defined as follows: premature, in particular those suffering from bronchial dysplasia-type after effects and children with congenital heart disease, congenital immune deficit, pulmonary, neurological or neuromuscular disease or a chronic condition.</u>	This population is not quantifiable. It should relate to only a small number of persons compared to other recommended populations.	
4. <u>Persons staying in a convalescent home or in a social healthcare home, regardless of age.</u>	The average number of persons staying in a convalescent home or in a social healthcare home is unknown.	--
<u>Total of populations eligible for vaccination against seasonal influenza</u>		**Around 11.9 million**

‡ Estimate of the number of persons under the age of 65 years with a chronic condition for which the vaccine against seasonal influenza is recommended is extracted from data on the frequency of chronic conditions among beneficiaries under the general health insurance scheme on 31/12/2009 (www.ameli.fr). The number of people qualifying under the general health insurance scheme have been extrapolated to the French population on the assumption that beneficiaries under the general scheme represent around 84% of all Sickness Insurance beneficiaries (unpublished data).