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TRANSPARENCY COMMITTEE
Opinion
7 November 2012

**IMMUGRIP, suspension for injection in prefilled syringe, split virion
inactivated influenza vaccine**

B/1 0.5 ml prefilled glass syringe with needle (CIP code: 34009 333 855 0 7)

Applicant: PIERRE FABRE MEDICAMENT

INN	split virion inactivated influenza virus
ATC Code (2012)	J07BB02 (seasonal influenza vaccines)
Reason for review	Request by the Directorate-General for Health and the Social Security Directorate
List concerned	National Health Insurance (CSS L.162-17)
Indication concerned	"Prophylaxis of influenza"

01 BACKGROUND

► Following the update in February 2012¹ to the High Council for Public Health (HCSP) guidelines for seasonal influenza vaccination in certain populations, the Director-General for Health and the Director for Social Security referred the matter to the Committee, in order for the possibility of changing the terms of inclusion for influenza vaccines currently appearing in the decree of 10 June 2011 to be examined.²

► In view of new available data, in particular following the 2009 pandemic and the 2010-2011 influenza season, **in its opinion dated 16 February 2012 the HCSP recommends that the population eligible for seasonal influenza vaccination be extended, on a long-term basis, to the following groups:**

- **Pregnant women in any trimester of pregnancy;**
- **Obese individuals with a body mass index (BMI) ≥ 40 kg/m².**

This HCSP opinion is accompanied by a report detailing the arguments on which the guidelines are based.³

As a reminder, in its opinion⁴ of 29 December 2010, the HCSP had already recommended that pregnant women with no associated risk factors and obese individuals⁵ should be vaccinated against influenza for the 2010-2011 influenza season, speculating that the circulating A(H1N1)pdm09 virus had retained its pandemic characteristics as far as population type affected and aggressiveness were concerned. In accordance with that 2010 opinion, the HCSP had again recommended that these two populations should be vaccinated for the 2011-2012 influenza season,⁶ with the exception, however, of women in the first trimester of pregnancy due to limited efficacy and safety data.

► It should also be noted that pregnant women with risk factors for complications of influenza are already among the populations in which influenza vaccination is recommended and reimbursed (see decree of 10 June 2011).

02 THERAPEUTIC INDICATIONS

“Prophylaxis of influenza, especially in those who run an increased risk of associated complications.

Use should be based on official recommendations.”

This vaccine is indicated in adults and children from 6 months of age.

03 POPULATIONS AFFECTED BY THE EXTENSION OF INFLUENZA VACCINE REIMBURSEMENT

According to the HCSP guidelines, in view of the new data available and whatever the types and subtypes of influenza virus circulating, the following groups of people are now included in the population eligible for influenza vaccination:

¹ High Council for Public Health. Avis relatif à l'actualisation de la vaccination contre la grippe saisonnière dans certaines populations (femmes enceintes et personnes obèses). 16 February 2012.

² Decree of 10 June 2011 changing the list of medicinal products reimbursed by National Insurance.

³ High Council for Public Health. Vaccination contre la grippe saisonnière – Actualisation des recommandations pour les femmes enceintes et les personnes obèses. Collection Avis et Rapports. 16 February 2012.

⁴ High Council for Public Health. Avis relatif à l'actualisation de la stratégie vaccinale contre la grippe 2010-2011. 29 December 2010.

⁵ Obese individuals whose body mass index is ≥ 30 kg/m².

⁶ High Council for Public Health. Avis relatif à l'actualisation de la stratégie vaccinale contre la grippe 2011-2012. 13 July 2011.

03.1 PREGNANT WOMEN IN ANY TRIMESTER OF PREGNANCY

► Pregnancy is recognised as a predisposition to severe complications for the mother and fetus in cases of influenza virus infection.

In cases of influenza infection, several studies have shown an increased risk of hospitalisation due to pulmonary and cardiovascular complications in pregnant women in any trimester of pregnancy, and particularly from the second trimester of pregnancy onwards.^{7,8,9} These data were confirmed during the 2009 pandemic.^{10,11,12,13,14} An increased mortality rate in pregnant women with influenza, in comparison with pregnant women in the general population, was reported during the influenza A(H1N1)pdm2009 pandemic, particularly in the USA.^{15,16} However, French monitoring data collected during this pandemic did not demonstrate any increased risk of death in pregnant women hospitalised for influenza in France, in comparison with pregnant women in the general population.¹⁷

The impact of seasonal influenza on pregnancy is difficult to evaluate due to a lack of relevant data available. However, for the 2009 pandemic, the results of a British cohort study¹⁸ suggest an increased risk of perinatal infant mortality and premature delivery (before 32 weeks' gestation) in women hospitalised for influenza A (H1N1), in comparison with pregnant women in the general population.

► Furthermore, clinical studies have shown that the immune response to influenza vaccination in pregnant women is comparable to that obtained in non-pregnant women¹⁹ and that influenza vaccination reduces the risks of respiratory illness with fever observed in pregnant women.²⁰ Other studies have demonstrated that maternal influenza vaccination confers protection on neonates, who cannot be vaccinated before the age of 6 months, in particular reducing the risk of respiratory infections.^{20,21,22,23}

► In terms of safety, in April 2012 ANSM published a pharmacovigilance report on the use of influenza vaccines in pregnant women²⁴ exposed to the vaccines used during international vaccination campaigns in the 2009/2010 influenza A (H1N1) pandemic. These data supplement

⁷ Neuzil KM, et al. Impact of influenza on acute cardiopulmonary hospitalisation in pregnant women, *Am J Epidemiol.* 1998; 148 (11): 1094-102.

⁸ Cox S, et al. Hospitalizations with respiratory illness among pregnant women during influenza season. *Obstet Gynecol.* 2006; 107 (6): 1315-22.

⁹ Hartert T, et al. Maternal morbidity and perinatal outcomes among pregnant women with respiratory hospitalizations during influenza season. *American Journal of Obstetric Gynecology.* 2003; 189: 1705-12.

¹⁰ Fuhrman C, Bonmarin I, Bitar D, et al. Adult intensive-care patients with 2009 pandemic influenza A(H1N1) infection. *Epidemiol Infect.* 2011; 139 (8): 1202-9.

¹¹ Jamieson DJ, Honein MA, Rasmussen SA, et al. H1N1 2009 influenza virus infection during pregnancy in the USA. *Lancet* 2009; 374 (9688): 451-58.

¹² Creanga AA, et al. Severity of 2009 pandemic influenza A (H1N1) virus infection in pregnant women. *Obstet Gynecol.* 2010; 115: 717-26.

¹³ Campbell A, et al. Risk of severe outcomes among patients admitted to hospital with pandemic (H1N1) influenza. *CMAJ.* 2010; 182: 349-55.

¹⁴ Van Kerkhove MD, et al. Risk factors for severe outcomes following 2009 influenza A (H1N1) infection: a global pooled analysis. *PLoS Med.* 2011; 8(7): e1001053. Epub 2011 Jul 5.

¹⁵ Louie JK, et al. Severe 2009 H1N1 influenza in pregnant and postpartum women in California. *N Engl J Med.* 2010; 362 (1): 27-35.

¹⁶ Siston AM, et al. Pandemic 2009 influenza A(H1N1) virus illness among pregnant women in the United States. *JAMA.* 2010; 303 (15): 1517-25.

¹⁷ Dubar G, et al. French experience of 2009 A/H1N1v influenza in pregnant women. *PLoS One.* 2010; 5 (10).

¹⁸ Pierce M, Kurinczuk JJ, Spark P, Brocklehurst P, Knight M. Perinatal outcomes after maternal 2009/H1N1 infection: national cohort study. *BMJ.* 2011; 342: d3214.

¹⁹ Englund JA. Maternal immunization with inactivated influenza vaccine: rationale and experience. *Vaccine.* 2003; 21 (24): 3460-4. Review.

²⁰ Zaman K, Roy E, Arifeen SE, et al. Effectiveness of maternal influenza immunization in mothers and infants. *N Engl J Med.* 2008; 359 (15): 1555-64. Epub 2008 Sep 17. Erratum in: *N Engl J Med.* 2009; 360(6): 648. Breiman, Robert E [corrected to Breiman, Robert F].

²¹ Benowitz I, Esposito DB, Gracey KD, et al. Influenza vaccine given to pregnant women reduces hospitalization due to influenza in their infants. *Clin Infect Dis.* 2010; 51 (12): 1355-61.

²² Eick AA, Uyeki TM, Klimov A, et al. Maternal influenza vaccination and effect on influenza virus infection in young infants. *Arch Pediatr Adolesc Med.* 2011; 165 (2): 104-11.

²³ Tsatsaris V, Capitani C, Schmitz T, et al; Inserm C09-33 PREFLUVAC (Immunogenicity and Safety of an Inactivated Nonadjuvanted A[H1N1v] Influenza Vaccine in Pregnant Women) Study Group. Maternal immune response and neonatal seroprotection from a single dose of a monovalent nonadjuvanted 2009 influenza A(H1N1) vaccine: a single-group trial. *Ann Intern Med.* 2011; 155(11): 733-41.

²⁴ ANSM. "Bilan de pharmacovigilance et profil de sécurité d'emploi des vaccins grippaux chez la femme enceinte". April 2012. Available online at <http://ansm.sante.fr>.

the existing safety data in pregnant women vaccinated against seasonal influenza.^{25,26,20} Analysis of the national report on severe cases did not demonstrate any increased risk linked to influenza vaccination in France. The results of this analysis are consistent with publications reporting follow-up of pregnant women vaccinated in Europe and the USA.^{27,28,29,30} Note that only inactivated vaccines may be used in pregnant women, whatever the stage of pregnancy.

03.2 OBESE INDIVIDUALS WITH BMI ≥ 40 KG/M²

► Obesity is a risk factor for complications of respiratory infections, including influenza infections.^{31,32,33,34}

Several publications have shown that in cases of influenza infection, obese individuals with or without risk factors, and in particular individuals with a BMI ≥ 40 kg/m² (morbid obesity), have a greater risk of hospitalisation for respiratory complications, of admission to intensive care, of needing prolonged mechanical ventilation and, possibly, of death.^{35,36,37,38}

► There are few efficacy data for influenza vaccines in obese individuals and these are based on immunogenicity data. The results of a recent observational study³⁹ suggest that the immune response to the influenza vaccine is impaired in obese individuals in comparison with those who are not obese.

²⁵ Tamma PD et al. Safety of influenza vaccination during pregnancy. Am J of Obstetrics & Gyn 2009 December: 547-52.

²⁶ Munoz FM et al. Safety of influenza vaccination during pregnancy. Am J Obstet Gynecol 2005; 192: 1098-106.

²⁷ Moro PL et al. Adverse events following administration to pregnant women of influenza A (H1N1) 2009 monovalent vaccine reported to the vaccine adverse event reporting system. Am J Obstet Gynecol 2011; 205: 473-75.

²⁸ Eleventh pandemic pharmacovigilance weekly update. European Medicines Agency (EMA) 17 February 2010; <http://www.ema.europa.eu/pdfs/influenza/10239210en.pdf>.

²⁹ Oppermann M, Fritzsche J, Weber-Schoendorfer C, et al. A(H1N1)v2009: a controlled observational prospective cohort study on vaccine safety in pregnancy. Vaccine. 2012 Jun 22; 30 (30): 4445-52.

³⁰ Pasternak B, Svanström H, Mølgaard-Nielsen D, et al. Risk of adverse fetal outcomes following administration of a pandemic influenza A(H1N1) vaccine during pregnancy. JAMA. 2012 Jul 11; 308 (2): 165-74.

³¹ Koenig, SM. Pulmonary complications of obesity. Am J Med Sci 2001; 321(4): 249-79.

³² Jubber, AS. Respiratory complications of obesity. Int J Clin Pract 2004; 58 (6): 573-80.

³³ Baik I, et al. A prospective study of age and lifestyle factors in relation to community-acquired pneumonia in US men and women. Arch Intern Med 2000; 160 (20): 3082-88.

³⁴ Jedrychowski W, Maugeri U, Flak E, et al. Predisposition to acute respiratory infections among overweight preadolescent children: an epidemiologic study in Poland. Public Health 1998; 112 (3): 189-95.

³⁵ Diaz E, et al. Impact of obesity in patients infected with 2009 influenza A(H1N1). Chest 2011; 139 (2): 382-86.

³⁶ Morgan OW, et al. Morbid obesity as a risk factor for hospitalization and death due to 2009 pandemic influenza A(H1N1) disease. PLoS ONE 2010; 5: e9694.

³⁷ Kwong J, Campitelli MA, Rosella LC. Obesity and respiratory hospitalizations during influenza seasons in Ontario, Canada: a cohort study. Clin Infect Dis 2011; 53 (5): 413-21.

³⁸ Fezeu L, Julia C, Henegar A, et al. Obesity is associated with higher risk of intensive care unit admission and death in influenza A (H1N1) patients: a systematic review and meta-analysis. Obes Rev. 2011 Aug; 12 (8): 653-9.

³⁹ Sheridan PA, Paich HA, J Handy, et al. Obesity is associated with impaired immune response to influenza vaccination in humans. International Journal of Obesity (2012) 36, 1072 – 1077.

04 TRANSPARENCY COMMITTEE CONCLUSIONS

Taking into account all of this information, and after discussion and a vote, the Committee considers that:

04.1 ACTUAL BENEFIT

- Influenza is a very contagious acute viral disease. Complications, which are sometimes serious, can occur in elderly and/or vulnerable patients.
- This is a preventative treatment.
- The efficacy/adverse effects ratio is high in pregnant women. It cannot be established in obese individuals with a body mass index ≥ 40 kg/m².
- Vaccines play an important role in the prevention strategy for influenza and its complications.
- Public health benefit:

Influenza is a common and contagious illness that can be serious in some categories of patients (particularly those with comorbid conditions and/or aged over 65 years). It constitutes a moderate public health burden. In the subpopulations newly targeted by the HCSP guidelines (pregnant women and obese individuals), the burden can be considered to be low, as the influenza attack rate is similar to that estimated in the general population and the number of hospitalisations or serious complications reported in these populations is low, particularly in cases with no other associated risk factors for complications.⁴⁰

Reducing the morbidity and mortality rates from influenza during epidemics is a public health need. Improving seasonal influenza vaccination coverage is an established priority in the French Public Health Law of 9 August 2004 (target 39: achieve minimum vaccination coverage of 75% in all target groups).

In France, vaccination coverage for seasonal influenza, as estimated from reimbursement data from the National Health Insurance general scheme, has noticeably declined since the influenza pandemic in 2009. In people aged over 65 years, vaccination coverage has gone from 63.3% in 2009 to 53.8% in 2010 and 54.0% in 2011. Vaccination coverage in other target groups has also fallen in all age brackets: in children aged under 10 years, coverage has gone from 24.3% in 2009 to 13.8% in 2010 and 17.3% in 2011; in young people aged 10 to 19 years, from 28.1% in 2009 to 16.7% in 2010 and 19.5% in 2011; and in people aged 20 to 64 years, from 39.2% to 29.9% and 31.9% respectively.⁴¹

As the target of 75% vaccination coverage has not been reached, the public health need remains.

In pregnant women, the impact of vaccination on the risk of spontaneous abortion has not been established, and its impact on reducing febrile illness is low. In obese individuals, the only efficacy data are based on immunogenicity data. In these populations, no data are available on any reduction in complications or risks, including cardiovascular risks (ischaemic attacks and cerebrovascular accidents) associated with influenza.

Therefore, only a low impact on morbidity can be expected in vaccinated individuals.

Furthermore, in general terms, the public health impact of seasonal influenza vaccination remains dependent both on achieving sufficient vaccination coverage in the recommended populations, and on to what extent the protection conferred by the seasonal vaccine corresponds to the virus strains circulating.

Consequently, in the populations newly targeted by the updated HCSP guidelines, the public health benefit of influenza vaccines is low.

- There are many treatment alternatives.

⁴⁰ S Vaux et coll. Dynamique et impact de l'épidémie A(H1N1)2009 en France métropolitaine, 2009-2010. BEH 2010; (24-26): 259-264.

⁴¹ P Tuppin, S Choukroun, S Samson, A Weill, P Ricordeau, H Allemand. Vaccination contre la grippe saisonnière en France en 2010 et 2011 : diminution des taux de couverture et facteurs associés. Presse Med 2012; 41: 568-576.

Consequently, in the populations newly targeted by the updated HCSP guidelines, the Committee considers that the actual benefit of this vaccine is substantial.

04.2 TARGET POPULATION

The target population corresponding to the extension of the population eligible for seasonal influenza vaccination consists of:

- Pregnant women in any trimester of pregnancy:⁴²

On the basis of the annual birth rate, the number of pregnant women each year can be estimated to be around 800,000.

- Obese individuals with a body mass index (BMI) ≥ 40 kg/m²:

According to a national epidemiological study of overweight and obesity in adults,⁴³ the prevalence of morbid obesity (BMI ≥ 40 kg/m²) is around 1.2% in adults. As elderly people aged over 65 years are already reimbursed for influenza vaccination, the number of obese adults aged between 18 and 65 years affected by these new guidelines can be estimated to be around 480,000.

In children and adolescents, according to the 2006 national nutrition and health study,⁴⁴ the prevalence of obesity is around 3.5% in those aged 3-17 years. There is no standardised definition of morbid obesity in children and adolescents, and the term is ill-suited to this population. According to expert opinion, around 0.05% of French adolescents meet the definition of super obesity, defined in adults by a BMI ≥ 50 kg/m², which corresponds in adolescents to a BMI of around 40 kg/m². Considering that children and adolescents who are super obese are likely to receive a seasonal influenza vaccine, and that the prevalence of super obesity is 0.05% in this population, the number of obese children and adolescents targeted by these new guidelines can be estimated to be around 7,000.

Nonetheless, pregnant women and morbidly obese individuals (BMI ≥ 40 kg/m²) with certain diseases (e.g. asthma, diabetes) targeted by the previous HCSP guidelines are already reimbursed for influenza vaccination, and consequently should not be included in these estimates; their number, however, cannot be estimated.

Thus, the number of pregnant women and obese individuals with a BMI ≥ 40 kg/m² who are likely to receive an influenza vaccine under these new guidelines is estimated to be a maximum of 1,290,000.

04.3 TRANSPARENCY COMMITTEE RECOMMENDATIONS

The Committee considers that the extension of influenza vaccine reimbursement is justified in the populations newly targeted by the guidelines in the HCSP opinion of 16 February 2012:

- Pregnant women in any trimester of pregnancy;
- Obese individuals with a body mass index (BMI) ≥ 40 kg/m².

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Health Insurance in the new populations cited above and at the dosages in the Marketing Authorisation.

► **Proposed reimbursement rate:** 65%

⁴² "Bilan démographique 2011 : la fécondité reste élevée". Insee Première n°1385. January 2012.

⁴³ "Obépi 2012, enquête épidémiologique nationale sur le surpoids et l'obésité", Inserm, Kantar Health, Roche.

⁴⁴ HAS. "Overweight and obesity in children and adolescents". Good practice guidelines - Rationale - September 2011.