HAUTE AUTORITÉ DE SANTÉ

INFECTIOLOGY
New medicinal product
April 2015

BRIEF SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION

FLUENZ TETRA, tetravalent vaccine against seasonal influenza in children

No clinical benefit demonstrated in the influenza prevention strategy

Main points

- FLUENZ TETRA is a live attenuated, nasal vaccine with Marketing Authorisation in the prevention of influenza in children and adolescents aged between 24 months and 18 years.
- This is the first approved vaccine containing four influenza vaccine strains, two of type A (H1N1 and H3N2) and two of type B (Yamagata and Victoria), i.e. an additional type B strain compared with the available trivalent influenza vaccines.
- No clinical benefit over other vaccines has been demonstrated as a result of this addition.
- The immunogenicity of FLUENZ TETRA is non-inferior to that of the trivalent formulation FLUENZ.
- The addition of a second virus B strain is not expected to benefit public health.

Therapeutic use

- According to the French High Council for Public Health, vaccination against seasonal influenza is recommended in all persons aged 65 years and over and in the following special populations:
  - pregnant women, irrespective of the trimester of pregnancy;
  - persons aged 6 months and over with conditions that predispose to the occurrence of serious complications of influenza (cf. vaccination schedule);
  - obese persons (BMI ≥ 40 kg/m2);
  - persons staying in a convalescent home or living in nursing home accommodation;
  - the family of babies under 6 months with serious influenza risk factors (cf. vaccination schedule);
  - professionals in regular and prolonged contact with persons at severe risk of influenza, in particular healthcare professionals and airline flight crew.

Role of the medicinal product in the therapeutic strategy

FLUENZ TETRA can be used in children aged between 2 and 18 years in whom influenza vaccination is recommended.
Use of FLUENZ live attenuated trivalent vaccine is of particular benefit in primary vaccination against influenza, especially in very young children.

FLUENZ TETRA cannot be used for the vaccination of certain populations specified in guidelines (cf. SPC), since it:
- is contraindicated in immunocompromised children and adolescents and their families, being a live vaccine;
- must not be used in children and adolescents with severe asthma or wheezing episodes;
- must not be used in babies and infants under 24 months, for safety reasons associated with higher hospital admission rates and an increased frequency of wheezing episodes in this population.

Clinical data

- The clinical development of FLUENZ TETRA comprises just a single comparative immunogenicity study in children aged 2 to 17 years versus the trivalent formulation of this nasal vaccine, FLUENZ. In this study of approximately 2300 children and adolescents without risk factors:
  - the immunity induced by FLUENZ TETRA was non-inferior to that induced by FLUENZ, in terms of geometric mean titre of IHA antibodies (primary endpoint);
  - a weaker immune repose was observed towards the two type A strains, H1N1 and H3N2, than towards the type B strains. In particular, seroconversion rates were of the order of 40% for the type B strains and less than 10% for the type A strains. This reduced immune response was observed with both FLUENZ TETRA and FLUENZ.

This study does not allow any conclusions to be drawn about the impact of addition of a fourth strain in terms of protective efficacy against influenza.

- The clinical relevance of measuring serum antibody levels is questionable, given that this is a live vaccine that induces primarily local immunity through the production of IgA in the mucosa of the upper respiratory tract. There is currently no standardised, validated method that allows this IgA to be isolated and quantified. Clinical interpretation of the results of this study is therefore problematic, especially since no correlate of protection against influenza based on serum antibody titre has been established for these nasally administered live vaccines.
- The most frequently reported adverse effects are nasal congestion/runny nose, headache, loss of appetite and malaise. This profile is similar to that of FLUENZ.
- The safety has not been evaluated in at-risk paediatric populations, such as asthmatics and individuals with weakened immunity.

Special prescribing conditions

- This influenza vaccine is subject to medical prescription.

Benefit of the medicinal product

- The actual benefit* of FLUENZ TETRA is substantial.
- FLUENZ TETRA does not provide clinical added value** (CAV V) in the strategy for the prevention of influenza in the populations recommended by the French High Council for Public Health.
- Recommends inclusion on the list of reimbursable products for supply by pharmacists and for hospital use.

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This document was created on the basis of the Transparency Committee Opinion of 29 April 2015 (CT-13920) and is available at **www.has-sante.fr**

[i] * The actual benefit (AB) of a proprietary medicinal product describes its benefit primarily in terms of its clinical efficacy and the seriousness of the condition being treated. The HAS Transparency Committee assesses the AB, which can be substantial, moderate, low or insufficient for reimbursement for hospital use.

** The clinical added value (CAV) describes the improvement in treatment provided by a medicinal product compared with existing treatments. The HAS Transparency Committee assesses the degree of CAV on a scale from I (major) to IV (minor). A level V CAV means "no clinical added value".