HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

26 September 2007

RELENZA 5mg/dose, inhalation powder, in single-dose containers
20 single-dose containers with an inhalation device (DISKHALER) (CIP: 351 974-8)

Applicant: GLAXOSMITHKLINE
Zanamivir
List I

Date of Marketing Authorisation: 26 July 1999
MA Variations:

- 4 September 2001 and 10 November 2003: variation to the sections "Special Warnings and precautions for use", "Undesirable effects" and "Pharmacodynamic Properties" with regard to high risk populations; 17 October 2005: change in the "Undesirable Effects" section**.**
- 7 February 2007: extension of indication to influenza prophylaxis, extension of indication to curative treatment of children aged from 5 to 12 years and change, in particular, of the "Pharmacodynamic Properties" section (data in the child).

Reason for request: inclusion on the list of medicines reimbursed by National Insurance and approved for use by hospitals in the following indications:

- Curative treatment of influenza in adults and children from 5 years who risk complications of influenza* and for whom influenza vaccination is recommended or those who are living or staying in institutions** and presenting symptoms typical of influenza when influenza is circulating in the community. Treatment should be initiated within 36 hours of the onset of symptoms in the child and within 48 hours for adults.
- Post-exposure prophylaxis after contact with a clinically diagnosed case of influenza, when influenza is circulating in the community, in the following subjects:
  - adults and children aged over 5 years at high risk,
  - presenting a contraindication to influenza vaccine.

RELENZA is not a substitute for influenza vaccination.

* Subjects at high risk for influenza complications in whom influenza vaccination is recommended:
- Adults aged over 65 years (JO influenza vaccines of 7 September 2000)
- Adults and children from the age of 5 years with long term conditions initially entitling them to reimbursement of influenza vaccination (JO influenza vaccines of August 25, 1999): insulin-dependent diabetes mellitus, non-insulin-dependent diabetes mellitus in patients uncontrolled by dietary measures alone; invalidating stroke; severe chronic kidney disease and pure primary nephrotic syndrome; serious forms of neuromuscular disorders (including myopathy); cystic fibrosis; poorly tolerated congenital heart disease, severe heart failure and severe valvular heart disease; serious chronic respiratory insufficiency (including asthma on the list of long-term conditions); serious primary immune deficiency disorder requiring prolonged treatment, infection by human immunodeficiency virus (for HIV-contaminated subjects the most recent studies show that vaccination may cause a transient increase in viral load so that vaccination should not be systematically recommended); homozygous sickle cell anaemia (congenital haemolytic anaemia due to haemoglobinopathy); immunocompromised patients (in particular transplanted subjects, subjects treated by immunosuppressive agents).
- Adults and children aged 5 years and older for whom it was very recently decided to reimburse influenza vaccination (JO influenza vaccines of November 10, 2006): subjects with COPD, persistent moderate asthma,
- Children and adolescents (aged from 5 to 18 years) whose health status requires prolonged treatment by acetylsalicylic acid: primarily for complicated Kawasaki syndrome and juvenile chronic arthritis (JO influenza vaccines of November 10, 2006).

** Except for subjects for whom the regulations stipulate that medical expenses must be reimbursed by the organisations, departments or institutions concerned

Health Technology Assessment Division

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1 Active ingredient:

Zanamivir

1.2 Indication

Treatment of influenza

RELENZA is indicated for treatment of both influenza A and B in adults and children (≥ 5 years) who present typical influenza symptoms when influenza is circulating in the community.

Influenza prophylaxis

RELENZA is indicated for post-exposure prophylaxis of influenza A and B in adults and children (≥ 5 years) following contact with a clinically diagnosed case in a household. In exceptional circumstances, RELENZA may be used for seasonal prophylaxis of influenza A and B during a community outbreak (e.g. in case of a mismatch between circulating and vaccine strains and a pandemic situation).

RELENZA is not a substitute for influenza vaccination. The appropriate use of RELENZA for Influenza prophylaxis should be determined on a case-by-case basis depending on the circumstances and the population requiring protection.

The use of antivirals for the treatment and prophylaxis of influenza should take into consideration official recommendations, variability in the epidemiology, and the impact of the disease in different geographical areas and patient populations.

1.3 Dosage

Treatment of influenza

Treatment should begin as soon as possible, within 48 hours after onset of symptoms for adults, and within 36 hours after onset of symptoms for children.

RELENZA is for administration by oral inhalation only, using the Diskhaler device provided. One single-dose container should be utilised for each inhalation.

The recommended dose of RELENZA for treatment of influenza in adults and children aged 5 years and older is two inhalations (2 x 5 mg) twice daily for five days, providing a total daily inhaled dose of 20 mg.

Influenza prophylaxis

- Post-exposure prophylaxis

The recommended dose of RELENZA for influenza prophylaxis, after close contact with an infected person, is 2 inhalations (2 x 5 mg) once daily for up to 10 days. Treatment must begin as soon as possible and within 36 hours of contact with an infected subject.

- Seasonal prophylaxis

The recommended dose for influenza prophylaxis during an epidemic period is 2 inhalations (2 x 5 mg) once daily for up to 28 days.

- Impaired renal or hepatic function: No dose modification is required.

- Elderly subjects: No dose modification is required.

2. SIMILAR MEDICINAL PRODUCTS

2.1 ATC Classification (2007)

J	:	General anti-infective for systemic use
J05	:	Systemic antiviral agent
J05A	:	Direct-acting antiviral agent
J05AH	:	Neuraminidase inhibitor
J05AH01	:	zanamivir

2.2 Medicinal products in the same therapeutic category

Neuraminidase inhibitors: oseltamivir
TAMIFLU 75 mg, capsule
TAMIFLU 12 mg/ml, powder for oral suspension

2.3 Medicinal products with a similar therapeutic aim

Preventive treatments:

- Another antiviral, MANTADIX 100 mg capsule (amantadine), is indicated for prophylaxis of influenza exclusively due to influenza virus A.
- Influenza vaccines

Non-specific symptomatic medications: analgesics and antipyretics

3. REMINDER OF THE COMMITTEE'S OPINION AND CONDITIONS OF INCLUSION

Opinion of November 24, 1999 (in the curative treatment indication):

Taking into account all the data submitted by the firm, the committee estimates that the actual benefit of RELENZA is insufficient.

4. ANALYSIS OF NEW AVAILABLE DATA

4.1 New studies on the curative treatment of influenza

During the first review of RELENZA by the French Transparency Committee, the laboratory provided 3 randomised studies (see opinion of November 24th, 1999) versus placebo in the curative treatment of influenza, conducted in the general population on a total of 1,588 patients with flu symptoms. The primary endpoint was the median time to significant improvement of influenza symptoms.

The intention-to-treat analysis of the results for the primary endpoint for 2 of these 3 studies, showed a slight but significant difference of 1.5 days (range: 1.0 to 2.5 days).

In its new application, the company submitted the results of:

- 2 studies in the curative treatment of influenza on high risk populations (asthma or COPD comorbidity and elderly subjects),
- 1 study in the curative treatment of influenza in children aged from 5 to 12 years.

These studies formed the basis of the following changes to the SPC:

- 4 September 2001 and November 10, 2003: adverse effects and pharmacodynamic properties sections with regard to subjects with asthma or COPD and subjects aged over 65 years,
- 7 February 2007: extension of indication to curative treatment of children aged from 5 to 12 years.

- **NAI 30 008 Study: asthma and COPD comorbidities**

It is a randomised, double-blind, placebo-controlled study that evaluates the efficacy of RELENZA at the dosage of two 5-mg inhalations, twice daily for 5 days.

Enrolled patients were adults and adolescents over 12 years of age with asthma (history of airway obstruction ≥ 12% or asthma treated during the year before the study) or COPD (FEV_1 ≤ 80%) and who had a flu-like syndrome for less than 48 hours. After enrolment, the diagnosis of influenza was confirmed virologically (positive viral culture and seroconversion).

The primary efficacy endpoint was the median time required to obtain a significant improvement in influenza symptoms. An improvement was defined by the absence of fever (<37.8°C) or febrile sensation and by no or only mild symptoms such as headache, cough, myalgia and sore throat. The improvement observed for all these criteria had to be maintained for more than 24 hours.

It was planned to analyse the primary endpoint on the population with virologically confirmed influenza. Five hundred patients were planned in this study, including 70% with virologically confirmed influenza.

Results:
The study was conducted on 525 patients.
Most patients were asthmatic, 16% had COPD alone, 6% asthma and COPD and 11% of the patients had severe lung disease.

Influenza was confirmed virologically in 60% of patients and 23% of all the patients had been vaccinated against influenza (20% of confirmed cases of influenza).

Table 1: Results of study NAI 30 008 in terms of median time to improvement in influenza symptoms (days)

Populations analysed	Zanamivir	Placebo	Difference zanimivir-placebo	p
Patients with confirmed influenza (sample size)	5.5 (n=160)	7.0 (n=153)	- 1.5	0.009
ITT (sample size)	6.0 (n=262)	7.0 (n=263)	- 1.0	0.123 (NS)

In the population with virologically confirmed influenza, the difference between the 2 groups was significant (reduction in median time to improvement of influenza of 1.5 day compared to placebo).

These results were not confirmed in the ITT population (all enrolled patients with influenza symptoms), though as the study was not designed for such an analysis, these non-significant results only provide an indication. However, virological confirmation does not correspond to the situation in clinical practice and it would have been more relevant to design this study with an ITT analysis.

Among the secondary endpoints, the incidence of complications was analysed on the population with influenza confirmed by laboratory tests. No difference was observed between zanamivir and placebo, whatever the type of complication (complication requiring antibiotic therapy, a change in treatment of respiratory symptoms, or any type of complication).

- **Study NAI 30 012: patients aged over 65 years**

It is a randomised, double-blind, placebo-controlled study evaluating the efficacy of RELENZA at the dosage of 2 inhalations of 5 mg, twice daily for 5 days in a population of patients aged 65 years or more with influenza symptoms.

The primary endpoint was the median time required to obtain a significant improvement in influenza symptoms. An improvement was defined by the absence of fever (<37.8°C) or febrile sensation and by the absence or presence of only mild symptoms such as headache, cough, myalgia and sore throat. The improvement observed for all these criteria had to be maintained for more than 24 hours.

Results:
The study was conducted on 358 patients aged from 64 to 94 years (mean 73 years), vaccinated against influenza in 46% of cases. Influenza was confirmed virologically in 65% of cases (positive viral culture and seroconversion).

Table 2: Results of study NAI 30 012 for median time to improvement in influenza symptoms (days)

Population analysed	Zanamivir	Placebo	Difference zanamivir - placebo	p
Patients with confirmed influenza (sample size)	7.25 (n=120)	7.5 (n=114)	- 0.25	0.609 (NS)
ITT (sample size)	6.5 (n=191)	7.5 (n=167)	- 1.0	0.159 (NS)

There was no significant difference in the median time to improvement of influenza symptoms between the two groups.

- **Study NAI 30.009: children from 5 years**

It is a randomised, double-blind, placebo-controlled study evaluating the efficacy of RELENZA at the dosage of 2 inhalations of 5 mg, twice daily for 5 days in a population of children aged from 5 to 12 years.

The enrolled children had a flu-like syndrome for less than 36 hours (ITT). After enrolment, the diagnosis of influenza was confirmed virologically (positive viral culture and seroconversion).

The primary endpoint was the median time required to obtain a significant improvement in the symptoms of influenza. An improvement was defined by the absence of fever (<37.8°C) or febrile sensation and by no or only mild symptoms such as headache, cough, myalgia and sore throat. The improvement observed for all these criteria had to be maintained for more than 24 hours.

It was planned to analyse the primary endpoint on the population with virologically confirmed influenza.

Results:
The study enrolled 471 children, 2% of whom were vaccinated against influenza. Influenza was virologically confirmed in 73% of cases.

Table 3: Results of study NAI 30 009 in terms of median time to improvement in influenza symptoms (days)

Populations analysed	Zanamivir	Placebo	Difference zanamivir - placebo	p
Patients with confirmed influenza (sample size)	4.0 (n=164)	5.25 (n=182)	-1.25	<0.001
ITT (sample size)	4.5 (n=223)	5,0 (n=247)	- 0.5	0.011

There was a significant difference in the median time to improvement of influenza symptoms between the two groups. The reduction was 0.5 days for all enrolled patients (ITT) and the difference was more marked (- 1.25 days) in the sub-group of patients with confirmed influenza.

Among the secondary endpoints in children with influenza confirmed in the laboratory, there was no significant difference in the incidence of complications requiring medical attention within 28 days of the start of treatment between zanamivir and placebo.

4.2 Indication in influenza prophylaxis

The laboratory provided 4 studies in the new indication "influenza prophylaxis" (MA obtained in 2007):

- 2 in influenza prophylaxis among family contacts.
- 2 in influenza prophylaxis during an epidemic, the first on subjects not at risk for complications and the other on subjects at high risk for influenza complications (age ≥ 65 years or high risk disease).

▱ **Studies NAI 30 010 and NAI 30 031: prophylaxis for family contacts**

These are two randomised, double-blind, placebo-controlled studies evaluating the efficacy of RELENZA at the dosage of 2 inhalations of 5 mg, once daily for 10 days in a family population. The families comprised from 2 to 5 persons aged 5 years or more. They were randomised within 36 hours after the onset of one case of influenza in the family (index case).

The primary endpoint was the percentage of families with at least one additional case of symptomatic influenza in the family (contact case).

In study NAI 30 010, index cases were treated by RELENZA at curative doses (2 inhalations per day for 5 days). In study NAI 30 031, index cases were untreated.

After enrolment, each case of influenza (contact and index) was virologically confirmed by culture, seroconversion or PCR.

➢ Results of study NAI 30 010 (treated index cases):

This study enrolled 337 families, i.e. 321 index cases and 837 contact cases.
In 49% of families, influenza was virologically confirmed in the index case.

The percentage of families with at least one additional case of influenza was 4% (7/169) with zanamivir versus 19% (32/168) with placebo ($p<0.001$. RR=0.21. $CI_{95\%}$=[0.11; 0.43]), corresponding to a prophylactic efficacy of 79 %.

Among the secondary endpoints, the number of subjects with influenza (individual cases) was 7/414 (2%) in the zanamivir group and 40/423 (9%) in the placebo group (ITT).

➢ Results of study NAI 30.031 (untreated index cases):

This study enrolled 487 families, i.e. 321 index cases and 1291 contact cases.
In 58% of the families, influenza was virologically confirmed for the index case.

The percentage of families with at least one additional case of influenza was 10/245 (4%) with zanamivir versus 46/242 (19%) with placebo ($p<0.001$. RR=0.19, $CI_{95\%=}$ [0.10; 0.36]), corresponding to a prophylactic efficacy of 81%.

For the secondary endpoints:

- The number of subjects with influenza (individual cases) was 12/630 (9%) in the zanamivir group and 55/661 (2%) in the placebo group (ITT).
- The number of secondary complications of influenza (secondary endpoint) was 3 in the zanamivir group and 15 in the placebo group. The difference is not significant.

- **Studies NAIA 3 005 and NAI 30 034: Prophylaxis during an influenza epidemic**

These are two randomised, double-blind, placebo-controlled studies evaluating the efficacy of RELENZA at the dosage of 2 inhalations of 5 mg, once daily for 28 days during an epidemic period.

The enrolled patients were randomised within 5 days of the first cases of influenza in the community. They may or may not have been vaccinated against influenza.

After enrollment, each case of influenza was virologically confirmed by culture, seroconversion or PCR.

- Study NAIA 3 005:

The patients were non-institutionalised adults and had no comorbidity with a high risk for complications.

The primary endpoint was the percentage of unvaccinated subjects with symptomatic, and virologically confirmed, influenza type A or B.

- Study NAI 30 034:

Subjects were non-institutionalised patients aged 12 years with a comorbidity with a high risk for influenza complications (age 65 years or older with diabetes, chronic lung or cardiovascular disorders).

The primary endpoint was the percentage of vaccinated or unvaccinated subjects with symptomatic, virologically confirmed, influenza type A or B during the period of prophylaxis (D1 to D28).

- Results of study NAI 3 005 in patients with no risk for complications:

This study enrolled 1107 subjects, aged from 18 to 70 years (average age 28 years), of which 86% were not vaccinated against influenza.

Table 4: results of study NAI 3 005

	Zanamivir (n=473)	Placebo (n=475)	p
Number of confirmed cases of influenza in unvaccinated subjects (%)	11 (2)	28 (6)	0.009
Complications of influenza (confirmed)	2 (<1)	6 (1)	0.293 (NS)

In the unvaccinated population, the number of cases of confirmed influenza was lower with zanamivir than with placebo (p=0.009, RR=0.40. $CI_{95\%}$= [0.20; 0.76]), corresponding to a prophylactic efficacy of 60%.

No difference was observed in the number of complications of influenza between zanamivir and placebo (secondary endpoint).

- Results of study NAI 30 034 in patients with a high risk of complications:

This study enrolled 3,363 patients aged 12 to 94 years (mean 60 years), vaccinated against influenza in 67 % of cases. Risk factors for complications of influenza are described in table 5.

Table 5: risk factors in the patient population of study NAI 30 034

High-risk Group	Zanamivir (n=1678)	Placebo (n=1685)
Subject ≥ 65 years	946 (56 %)	950 (56 %)
Respiratory disease		
- Asthma	564 (34 %)	582 (35 %)
- COPD	147 (9 %)	139 (8 %)
Cardiovascular disease	331 (20 %)	307 (18 %)
Diabetes		
- insulin-dependent	127 (35 %)	108 (29 %)
- non insulin-dependent	232 (65 %)	261 (71 %)

Table 6: Results of study NAI 30 034

Endpoint	Zanamivir (n=1678)	Placebo (n=1685)	p
Number of confirmed cases of influenza in vaccinated and unvaccinated subjects (%)	4 (0.2%)	23 (1.4%)	<0.001
Complications of influenza (secondary endpoint)	1 (<0.1)	8 (<1)	0.042

In the population of vaccinated and unvaccinated patients, the number of cases of confirmed influenza was lower with zanamivir than with placebo ($p<0.001$, RR=0.17. $CI_{95\%}$= [0.07; 0.44], corresponding to a prophylactic efficacy of 83%.

A significant difference was observed in favour of zanamivir for the incidence of complications of influenza.

It should be stressed that in the two studies carried out during an influenza epidemic, the number of cases of influenza observed during the study period was very low. This is probably explained by the fact that these studies were carried out during a relatively mild epidemy.

4.3 Safety

Safety analysis in the new studies does not modify the safety profile of zanamivir established during the first opinion by the French Transparency Committee in 1999.

Since the previous Transparency Committee opinion, new wording was added to the adverse effects section of the SPC in 2000: “There have been rare reports of patients with previous history of respiratory disease (asthma, COPD) and very rare reports of patients without previous history of respiratory disease, who have experienced acute bronchospasm and/or serious decline in respiratory function after use of RELENZA”.

The adverse effects mentioned in the SPC are very rare (incidence < 1/10 000).

4.4 Resistance

No viral strain with a reduced sensitivity to zanamivir has yet been detected during clinical trials. However, according to the model of resistances occurring with oseltamivir for which there is a longer follow-up, it may be supposed that the wider use of zanamivir will cause the emergence of resistant influenza viruses. Resistance emergence must therefore be monitored.

In vitro, cross-resistance was observed in certain mutant influenza viruses resistant to zanamivir and mutant influenza viruses resistant to oseltamivir. It will be necessary to test for cross-resistance to oseltamivir and zanamivir in clinical practice.

4.5 Conclusion

In the indication for curative treatment of influenza:

In this indication, 3 new studies, posterior to the opinion of November 24th, 1999, were provided. These concerned populations at high risk of complications (patients with underlying asthma or COPD, elderly patients) and children aged from 5 years.

In subjects with asthma or COPD, zanamivir induced a slight reduction in the duration of symptoms of influenza in comparison with placebo (median of 1.5 days) only in the population with virologically confirmed influenza (population selected for the analysis of the primary endpoint). This effect was not confirmed in the ITT population although it is this population that will be treated in practice. A study planning an ITT analysis would therefore have been more relevant. No efficacy was observed on the reduction in complications.

In subjects aged 65 years or more, no significant difference was observed for the median time to improvement of influenza symptoms.

In children aged 5 to 12 years, zanamivir gave a slight reduction in the duration of influenza symptoms versus placebo. The median reduction in the duration of symptoms was 0.5 days by the ITT analysis (real treated population) and 1.25 days in the sub-group of patients with confirmed influenza. No efficacy was observed on the reduction in influenza complications in the child.

There was a significant difference in the median time to improvement of influenza symptoms between the two groups. The reduction was 0.5 days for all enrolled patients (ITT).

In the indication for influenza prophylaxis:
During the 2 studies in a family population aged 5 years or more with no risk factors for complications and with one case of influenza in the household, the prophylactic efficacy of zanamivir at family level was 79% and 81%. The reduction in the number of influenza complications was not significant.

In a study of prevention during an epidemic for 28 days in vaccinated or unvaccinated adult patients, without a high risk of complications, zanamivir reduced the number of cases of influenza compared to placebo (11/473 with zanamivir versus 28/475 with placebo, p = 0.009).

A second study during a relatively mild influenza epidemic was carried out during 28 days in vaccinated and unvaccinated patients at high risk for complications of influenza. This study showed a reduction in the number of cases of influenza with zanamivir compared to placebo (4/1678 with zanamivir versus 23/1685 with placebo, p <0.001).

5. TRANSPARENCY COMMITTEE CONCLUSIONS

5.1 Actual Benefit

Prior definitions:

Subjects “at high risk” are defined as subjects aged over 65 years or subjects belonging to the one of the 11 categories below (9 long-term conditions and 3 other categories) entitled to the reimbursement of influenza vaccine:

- Insulin-dependent diabetes mellitus, non-insulin-dependent diabetes mellitus uncontrolled by dietary measures alone;
- Invalidating stroke;
- Severe chronic kidney disease and pure primary nephrotic syndrome;
- Serious form of a neuromuscular disorder (including myopathy);
- Cystic fibrosis;
- Poorly tolerated congenital heart disease, serious heart failure and serious valvular heart disease;
- Serious chronic respiratory insufficiency (including asthma on the long-term condition list)
- Serious primary immune deficiency disorder requiring prolonged treatment, infection by human immunodeficiency virus (for HIV-contaminated subjects the most recent studies show that vaccination may cause a transient increase in viral load so that vaccination should not be systematically recommended)
- Homozygous sickle cell anaemia (congenital haemolytic anaemia due to haemoglobinopathy);
- Patients with asthma and COPD;
- Persons staying in a medium or long-stay health institution of whatever age;
- Children and adolescents (aged from 1 to 18 years) whose health status requires prolonged treatment by acetylsalicylic acid.

Influenza is a highly contagious, acute viral disease which, in most cases, is not serious and spontaneously resolves in about 1 week. However, in certain subjects, influenza complications may be serious and life-threatening.

In children, the clinical picture of influenza is all the less typical when the child is young. Children are the first to be affected during an epidemic.

The complications of influenza are particularly serious in infants (RELENZA is not indicated in this population) and in children with a comorbidity (asthma in particular).

There are usually no serious complications in healthy children over 5 years of age. The most frequent complications are respiratory and ENT disorders, otitis in particular. The incidence of these complications decreases with age.

Vaccination against influenza is the cornerstone of management of this disease. It is particularly recommended for subjects at high risk of complications and for health care providers.

RELENZA is intended as both a curative and preventative antiviral therapy (post-exposure prophylaxis).

The actual benefit of zanamivir is limited for the following reasons:

- The probabilistic nature of the diagnosis of influenza, especially when the subject is young,
- The need to administer treatment within 36 hours of first symptoms (or 48 hours depending on the case) for it to be effective,
- The method of administration by inhalation; the system of administration is likely to be misused by certain patients, in particular elderly subjects and children.

5.1.1 Actual benefit in the indication curative treatment of influenza

Public health benefit:

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

Reducing the morbidity and mortality of influenza during epidemics is a public health need. This need is generally covered by vaccination. However, an additional therapy may be useful in high risk subjects (comorbidity and/or age over 65 years in particular) who contract influenza despite vaccination.

The expected impact of this product in terms of morbidity and mortality cannot be quantified from the clinical study data because of the lack of mortality data and the small size of the effect on morbidity criteria.

Moreover, it is difficult to extrapolate the results of these studies as they are dependent on the organisation of care (real vaccine coverage, time before initiation of treatment in actual practice).

Therefore, RELENZA should not provide a significant answer to an identified public health need.

Consequently, RELENZA is not expected to benefit public health.

▫ Children (5 to 11 years) not belonging to a high risk population:

When zanamivir was taken within 36 hours of the onset symptoms, it provided a slight reduction in the duration of symptoms (median value of 0.5 day in the ITT analysis). No benefit was demonstrated on the reduction in complications.
Adverse effects were very uncommon.

The efficacy/safety ratio was low.

The actual benefit of RELENZA for curative treatment of children aged from 5 to 11 years without comorbidity is insufficient.

- Adolescents (≥ 12 years) and adults (< 65 years) not belonging to a high risk population:

The submitted data are insufficient to change the previous committee opinion. The actual benefit of RELENZA for curative treatment of adolescents (≥ 12 years) and adults (< 65 years) is insufficient.

- Adolescents (≥ 12 years) and adults (< 65 years) with asthma or COPD comorbidities:

Zanamivir induced a slight reduction in the duration of influenza symptoms (median of 1.5 days) versus placebo in the population with influenza confirmed by laboratory tests (population retained for the analysis of the primary endpoint). This effect was not confirmed in the ITT population. However it is this population that will be treated in practice. No efficacy was observed for the reduction of complications.

The actual benefit of RELENZA for curative treatment of teenagers (≥ 12 years) and adults (< 65 years) with asthma or COPD comorbidities is insufficient.

- Elderly (> 65 years):

No significant difference was demonstrated relative to placebo.
The actual benefit of RELENZA for curative treatment in the elderly (>65 years) is insufficient.

5.1.2 Actual benefit for post-exposure prophylaxis in adults and children aged from 5 years

RELENZA may be used for influenza prophylaxis in adults and children aged from 5 years after close contact with a clinically diagnosed case in the household. Prevention should be initiated as soon as possible, within 48 hours of the onset of symptoms in adults, and within 36 hours after onset of symptoms in children. Protection only lasts for the duration of treatment.

Public health benefit:

The burden due to influenza in children aged over 5 years and adults may be considered to be moderate. However, taking into consideration flu vaccine coverage and the relatively small number of patients concerned by the indication (prophylaxis after contact with a clinically diagnosed case), the burden is low.

Reducing the morbidity and mortality of influenza during epidemics, in particular in high-risk patients, is a public health need.

Considering the data obtained during clinical studies and despite the lack of data on mortality, this proprietary medicine is expected to have a moderate impact in terms of morbidity and mortality. However, it is difficult to extrapolate the results of these studies as they are dependent on healthcare organisation (real vaccine coverage, time before initiation of treatment in actual practice etc.) Moreover, there is a risk that RELENZA may have a negative effect on public health and morbidity and mortality by reducing vaccine coverage after its marketing.

Hence, taking into account these reservations, the product RELENZA should provide an additional response (complementary to vaccination and non-medical measures) to an identified public health need.

Accordingly, RELENZA is expected to benefit public health in this indication. This benefit is low.

In the very rare situations when vaccine protection is not ensured by the vaccine (mismatch between the vaccine and circulating viral strain), neuraminidase inhibitors including RELENZA, may have a specific public health benefit.

▫ Population not at high risk for complications:

During 2 studies in a family population composed of subjects aged 5 years or more with no risk factors for complications and with one case of influenza in the household, the number of families with at least 1 contact case of influenza was lower with zanamivir than with placebo. The protective efficacy of zanamivir was 79% (treated index case) and 81% (untreated index case). The reduction in the number of secondary influenza complications was not significant.

In an adult population, during an epidemic, zanamivir reduced the number of contact cases of influenza compared to placebo in the sub-group of vaccinated patients (11/473 on zanamivir versus 28/475 on placebo, p = 0.009). These results were confirmed in the ITT population.
Taking into account the fact that, in this population, influenza is usually benign and vaccine efficacy high, the actual benefit of RELENZA for influenza prophylaxis in subjects without comorbidities is insufficient.

▫ Population at high risk for complications:

In a population of adolescents (≥ 12 years) and adults, during an epidemic, zanamivir reduced the number of contact cases of influenza compared to placebo (4/1678 with zanamivir versus 23/1685 with placebo, p <0.001). These results must be considered with caution insofar as these results were obtained during a mild epidemic.
No data are available for children.
Taking into account:

- The studies presented in high risk populations (age ≥ 65 years, asthma and COPD, cardiovascular disorders, diabetes),
- The risk of serious complications in these populations,
- The lower efficacy of the influenza vaccine in adults aged over 65 years,

the actual benefit of RELENZA for post-exposure prophylaxis in high risk populations is low.

In addition, in subjects at high risk, and in particular in the following cases:

- Subjects living in institutions (institutionalised patients)
- Subjects with a contraindication to the vaccine
- Immunocompromised subjects (in particular subjects with AIDS, an organ transplant or those treated by immunosuppressive drugs)
- Situations in which the vaccine only provides partial protection from the circulating strain.

the actual benefit of RELENZA in post-exposure prophylaxis is moderate.

Taking into account the risk of potentially serious complications in these populations, the Committee estimates that RELENZA may benefit these subjects.

5.2 Improvement in actual benefit

RELENZA provides no improvement in actual benefit (IAB V) in influenza prophylaxis compared to TAMIFLU.

5.3 Therapeutic use

Because of epidemiological arguments in favour of the reduction in influenza complications, hospital admissions and deaths of vaccinated subjects compared to unvaccinated subjects, vaccination against influenza constitutes the reference strategy for the management of influenza and prophylaxis in high-risk groups.

In patients with an influenza syndrome, the reference symptomatic treatment is nonspecific and is based on a combination of antipyretics and analgesics.
The value of antiviral agents (oseltamivir and zanamivir) for the symptomatic treatment of influenza in a normal epidemic setting is limited.

During an epidemic, anti-influenza viral agents (oseltamivir and zanamivir) may be used after contact with a subject with flu syndrome. Treatment must be initiated as early as possible after exposure and not later than 48 after the first symptoms in the subject with flu symptoms. The protective efficacy lasts the time of treatment.

Prophylactic treatment is short lasting (maximum 6 weeks for oseltamivir and 4 weeks for zanamivir). Hence during an epidemic, late vaccination is still recommended.

In this situation, after contact with a subject with flu syndrome, the prophylactic use of zanamivir or oseltamivir is particularly recommended in subjects at high risk for complications who are only partially protected or not protected by the vaccine:

- Subjects aged over 65 years,
- Subjects vaccinated for less than 15 days,
- Subjects in whom vaccination is contra-indicated,
- Mismatch between the vaccine strain and circulating viral strain.

When an epidemy is declared during the period of flu virus circulation and it has been documented in health care facilities, including hospitals caring for high-risk subjects, it is recommended that[1]:

- Post-exposure prophylaxis is initiated within 48 hours after the contact with a person presenting flu syndrome in all high-risk subjects aged from 1 year, whether they were vaccinated or not,
- This treatment is prescribed for up to 7 days after the onset of symptoms in the latter case.

The choice of antiviral agent must take into account the pharmaceutical form: capsule or inhalation using the ROTADISK device. The inhalation device may be misused, so that the inhaled doses are insufficient. This problem is certainly more frequent in very elderly persons and children.

5.4 Target population

The populations in whom the Committee considered that the actual benefit of RELENZA for post-exposure prophylaxis was sufficient to justify reimbursement are high-risk subjects i.e.:

- Subjects aged over 65 years,
- Subjects aged from 5 to 65 years:
  - with one of the 9 long-term conditions qualifying for reimbursement of influenza vaccine,
  - with asthma and chronic obstructive pulmonary disease (outside long-term condition status),
  - staying in a long or medium-term health care facility,
  - Children and adolescents (aged from 5 to 18 years) whose health status requires prolonged treatment by acetylsalicylic acid.

It is therefore necessary to quantify among these subjects, the population of persons within a household who may come in contact with someone with flu syndrome and should therefore receive prophylactic treatment by RELENZA within not more than 48 hour of exposure.

<u>The target population may be estimated from the following data and assumptions:</u>
<u>Demographic data:</u>

- Number of subjects aged over 65 years: 10,111,093 (INED 2007)
- Number of subjects aged from 5 to 64 years with comorbidities (long-term conditions): 1,307 million (CNAMTS 2003)
- Number of subjects with asthma and COPD aged from 5 to 64 years:
  - *o* Prevalence of asthma of 5.8% (CREDES 2000), i.e. approximately 2.8 million persons,
  - *o* The number of subjects with COPD before the age of 65 years and without a long-term condition may be considered to be negligible.

[1] According to the opinion of French Higher Public Health Advisory Board on prophylaxis in institutionalised persons at high-risk during an influenza epidemic when influenza is circulating in the community. Session of January 16 2004

- Number of children and adolescents (from 1 to 18 years) whose health status requires prolonged treatment by acetylsalicylic acid: negligible in comparison with the previous populations.

Epidemiological data on influenza in these populations[2]:

- Incidence of influenza
  - *o* Subjects aged from 5 to 64 years: approximately 4 %
  - *o* Subjects aged over 65 years, approximately 0.3 %

Data on the distribution of these subjects in terms of households: (INSEE 2002)

Among those subjects aged over 65 years living at home:

- Subjects over 65 years in age and living alone: 30%
- Subjects over 65 years living in a household of at least 2 people: 70%
  Including approximately:
  - 70% living together with a person of the same age
  - 15% living in households of 2 persons with an adult of from 13 to 64 years
  - 15% living in households of 3 persons with 2 adults of from 13 to 64 years
- The number of institutionalised subjects aged 65 years or more may be estimated to be 500,000 to 550,000

In addition: subjects with comorbidities aged from 5 to 64 years:

- Assumption of a homogeneous distribution of these subjects in French households
- Mean household size of 3 persons (including 2 contact cases)

Data on the time to initiate treatment after contact (48 hours):

This parameter is derived from the data collected for symptomatic treatment.
These show that 50 to 80% of subjects see their doctor for flu syndrome within 48 hours of its onset. The assumption is made that these percentages may be extrapolated to the prophylactic treatment of non-institutionalised subjects.
However for institutionalised subjects, it is considered that prophylactic treatment may be administered to 100% of subjects within 48 hours.

Results:
Interim calculations made according to these assumptions, show that:
- The number of potential contact cases among non-institutionalised subjects over 65 years is between 90,000 and 150,000.

- The number of potential contact cases among subjects from 13 to 64 years with comorbidities is between 160,000 and 260,000.

- The number of potential contact cases among subjects in medium and long stay institutions may be estimated to be more than 550,000.

In the specific cases cited above in which the actual benefit was evaluated to be moderate, the number of potential contact cases is smaller than the other populations.

Immunocompromised subjects:

- Prevalence of cases of AIDS in 2005: between 26,000 and 28,500 subjects[3]
- Prevalence of transplanted subjects: 4,428 organ transplants and 4,326 patients underwent haematopoietic stem cell transplantation in 2006 (2006 assessment by the Biomedecine Agency)

Contraindication to vaccination: extremely small population.

[2] Data of the Sentinelles network (mean values for the years 2003 to 2006).
[3] Population already included in the total population of contact cases of subjects with one of the 9 comorbidities.

5.5. Transparency Committee Recommendations

The Transparency Committee does not recommend inclusion on the list of medicines reimbursed by National Insurance and on the list of medicines approved for use by hospitals and various public services in the indication: treatment of influenza.

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Insurance and on the list of medicines approved for use by hospitals and various public services in the indication: post-exposure influenza prophylaxis for high-risk subjects, at the dosage of the MA:

- Persons aged over 65 years
- Persons aged from 5 to 65 years with one of the 5 long-term conditions qualifying for reimbursement of influenza vaccine,
- Patients aged from 5 years with asthma and COPD,
- Children and adolescents (aged from 5 to 18 years) whose health status requires prolonged treatment by acetylsalicylic acid: primarily for complicated Kawasaki syndrome and juvenile chronic arthritis
- Persons staying in a medium or long-stay health care facility, whatever their age,

The Commission would like a follow-up study to be set up for patients in whom prophylactic treatment by RELENZA is initiated. The objectives of this survey are to document in a clinical setting:

- The profile of treated patients (socio-demographic data, medical history, vaccine status etc.)
- The transposability of RELENZA treatment modalities, in particular the setting in which treatment is instituted (post-exposure to a family case, during an epidemic etc), time between exposure and institution of treatment after contact and the correct use of this dosing system (DISKHALER), in particular by elderly subjects.
- Impact on the clinical outcome of patients : occurrence of influenza (with precision about virological confirmation or not), occurrence of complications, mortality etc.

In the case in which scheduled or on-going studies, in particular within the scope of European Risk Management plan, do not answer all the questions raised by the Transparency Committee, a specific study must be conducted.

The duration of the study must be justified by an independent scientific committee.

5.5.1 Packaging: Appropriate for the prescription conditions

5.5.2 Reimbursement rate : 35 %