HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

4 November 2009

SINGULAIR 4 mg chewable tablets
Pack of 28 (CIP: 393 112-4)
Pack of 50 (CIP: 393 118-2)

SINGULAIR 4 mg granules
Pack of 28 single dose sachets of 4 mg (CIP: 393 123-6)

Applicant: MSD - CHIBRET

montelukast

ATC Code: R03DC03

List I

Marketing authorisation date: 27 March 2009

Reason for request: Inclusion on the list of medicines reimbursed by National Insurance and approved for use by hospitals.

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

montelukast

1.2. Indication

“SINGULAIR is indicated as add-on treatment for asthma in those patients with mild to moderate persistent asthma inadequately controlled on inhaled corticosteroids and where “as-needed” fast and short-acting beta-2 adrenergic agonists do not provide adequate clinical control.

SINGULAIR is also indicated in the prophylaxis of exercise-induced asthma.

SINGULAIR may also provide an alternative to low-dose inhaled corticosteroids in patients with mild persistent asthma, without a recent history of severe asthma attacks requiring treatment with oral corticosteroids and who have demonstrated the inability to observe inhaled corticosteroid treatment.”

1.3. Dosage

“This product must be administered to children under adult supervision.”

Specific information on granules:

“In children aged 6 months to 5 years, the recommended dosage is one 4 mg sachet of granules per day, in the evening. No dosage adjustment is required in this age group. Efficacy data from clinical trials on children aged 6 months to 2 years with persistent asthma is limited. The response to treatment with montelukast must be evaluated after 2 to 4 weeks, and treatment should be discontinued when there is no response. SINGULAIR 4 mg granules must not be given to children under 6 months.

Administering SINGULAIR granules:

SINGULAIR granules may be taken directly in the mouth or mixed with a spoonful of preferably semi-liquid food, cold or at room temperature (e.g. apple purée, ice-cream, carrots or rice). The sachet should not be opened in advance. After opening, the entire dose of SINGULAIR granules must be administered immediately (within 15 minutes). If the SINGULAIR granules are mixed with food, they must not be stored for later use. The SINGULAIR granules should not be dissolved in liquid. However, the patient may drink after taking the granules. The SINGULAIR granules can be taken during or between meals.”

Specific information on chewable tablets:

“A granule formulation is available for children who have difficulty taking the chewable tablets (see SINGULAIR 4 mg granules SPC).

In children aged 6 months to 5 years, the recommended dosage is one 4 mg chewable tablet per day, in the evening. The product should be taken at least one hour before or two hours after mealtimes. No dosage adjustment is required in this age group. SINGULAIR 4 mg chewable tablets must not be given to children under 2 years old.”

Information concerning both forms:

"General recommendations:
SINGULAIR has an effect on asthma symptoms within one day. Patients should be advised to continue their treatment even if their asthma is under control, as well as when symptoms worsen.
No dose adjustment is necessary in patients with mild to moderate hepatic impairment or renal impairment. No data is available on patients with severe hepatic impairment. The dosage is the same for both male and female patients.

SINGULAIR used as an alternative to low-dose inhaled corticosteroids for mild persistent asthma:
Montelukast is not recommended on its own in patients with moderate persistent asthma. Using montelukast as an alternative to low-dose inhaled corticosteroids should only be considered for children aged 2 to 5 with mild persistent asthma with no recent severe asthma attacks requiring oral corticosteroid therapy and who have demonstrated the inability to observe inhaled corticosteroid therapy (see section 4.1). Mild persistent asthma is characterised by daytime symptoms occurring more than once a week but less than once a day, nighttime symptoms more than twice a month but less than once a week, with normal pulmonary function between attacks. If during the check-up the patient's asthma is deemed to be inadequately controlled (usually during the following month), treatment with an additional or different anti-inflammatory drug must be considered using a gradual management method. Asthma control must be assessed regularly in these patients.

SINGULAIR used as preventive treatment of exercise-induced asthma in children aged 2 to 5:
In children aged 2 to 5, exercise-induced bronchoconstriction can be the predominant manifestation of persistent asthma requiring inhaled corticosteroid treatment. The response to montelukast treatment should be evaluated after 2 to 4 weeks. If the effect is inadequate, additional or alternative treatment should be considered.

Administration of SINGULAIR with other asthma treatments:
When SINGULAIR is used as a treatment to supplement inhaled corticosteroids, it is not appropriate to substitute the inhaled corticosteroids abruptly (see section 4.4).
10 mg film-coated tablets are available for adults and adolescents over 15.
5 mg chewable tablets can be used for children aged 6 to 14."

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2009)

R : Respiratory system
R03 : Drugs for obstructive airway diseases
R03D : Other systemic drugs for obstructive airway diseases
R03DC : Leukotriene receptor antagonists
R03DC03 : montelukast

2.2. Medicines in the same therapeutic category

2.2.1. Strictly comparable medicinal products

SINGULAIR 4 mg is the only leukotriene receptor antagonist indicated for the treatment of children aged 6 months to 5 years with asthma.

2.2.2. Medicinal products that are not strictly comparable

SINGULAIR 5 mg and 10 mg are indicated for children over the age of 6 and adults.

2.3. Medicines with a similar therapeutic aim

- Medicines used for single constitutional treatment in children with mild persistent asthma:

Active ingredient	**Product**	**Dosage:**
beclomethasone	NEXXAIR 100 µg suspension for inhalation QVAR AUTOHALER 100 µg solution for inhalation BECOTIDE 50, 250 µg solution for inhalation PROLAIR 250 µg powder for inhalation	from the age of 4 from the age of 4 for children for children
budesonide	PULMICORT 100 µg, 200 µg suspension for inhalation PULMICORT 100 µg, 200 µg TURBUHALER powder for inhalation MIFLONIL 200 µg powder for inhalation	for children for children for children
fluticasone	FLIXOTIDE 50 µg, suspension for inhalation FLIXOTIDE Diskus 100 µg powder for inhalation	1 to 4 years from the age of 4

- Medicines used for ongoing treatment in a fixed or non-fixed combination with inhaled corticosteroids for children with mild to moderate persistent asthma inadequately controlled with inhaled corticosteroid treatment and “as-needed” fast and short-acting beta-2 adrenergic agonists:

Active ingredient	**Product**	**Dosage:**
salmeterol	SEREVENT 25 µg /dose suspension for inhalation SEREVENT DISKUS 50 µg/dose powder for inhalation SISEROL 25 µg /dose suspension for inhalation* SISEROL DISKUS 50 µg/dose powder for inhalation*	from the age of 4 from the age of 4 from the age of 4 from the age of 4
salmeterol/fluticasone	SERETIDE 50/25 µg suspension for inhalation	from the age of 4

*: not marketed

- Medicines indicated in the prevention of exercise-induced asthma in children:

- short-acting beta-2 agonists and anticholinergic products:

Active ingredient	**Product**	**Dosage:**
salbutamol	BUVENTOL EASYHALER 100 µg VENTOLIN 100 µg AIROMIR 100 µg Autohaler ASMANAL Clickhaler 90 µg VENTODISK 200 µg	from the age of 4 no age limit no age limit no age limit no age limit
terbutaline	BRICANYL 250 µg, 500 µg	no age limit
fenoterol / ipratropium	BRONCHODUAL powder for inhalation	no age limit

- long-acting beta-2 agonists:

Active ingredient	Product	Dosage:
salmeterol	SEREVENT 25 µg /dose suspension for inhalation SEREVENT DISKUS 50 µg/dose powder for inhalation SISEROL 25 µg /dose suspension for inhalation* SISEROL DISKUS 50 µg/dose powder for inhalation*	from the age of 4 from the age of 4 from the age of 4 from the age of 4

*: not marketed

3 ANALYSIS OF AVAILABLE DATA

The company's request is based on:

1. clinical and pharmacokinetics data from the clinical development of SINGULAIR 4 mg:
   - the bioequivalence of the tablet and granule forms for adults and validation of the 4 mg dose (MA file). These studies will not be described in this opinion.
   - placebo-controlled safety study on children aged 6 months to 2 years, where efficacy was the secondary endpoint (study PN176[1]), and its extension (study PN232)
   - safety study on children aged 2 to 5, where efficacy was a secondary endpoint (study PN072[2]), and its extension (study PN072-20)
   - placebo-controlled study (PREVIA study[3]) of children aged 2 to 5 with a history of asthma attacks induced by an acute viral infection.
2. data from literature:
   - study comparing inhaled budesonide to montelukast in children aged 2 to 8 with mild persistent asthma or recurring bouts of wheezing (Szefler study, 2007[4])
   - four placebo-controlled studies on small series of patients (not described below).

3.1. Efficacy

Placebo-controlled study of children aged 6 months to 2 years (PN176)

Randomised (2:1), double-blind study comparing montelukast 4 mg to placebo for 6 weeks in children aged 6 months to 2 years diagnosed with asthma or asthma-like symptoms. The primary objective of this study was to evaluate safety and the secondary objective was to evaluate efficacy.

Patients must have had at least 3 asthma attacks from the age of 8 weeks with at least one attack over the 6 months prior to inclusion and must have used short-acting beta-2 agonists at least twice a week over the month prior to inclusion.

The treatments were administered in one intake in the evenings over 6 weeks. Patients could take short-acting beta-2 agonists in the event of an attack and continue corticosteroid or cromone treatment in inhaled or nebulised form if the latter were administered for at least 2 weeks prior to inclusion, at a steady dose maintained throughout the study.

[1] Van Adelsberg J, et al. Safety, tolerability, and exploratory efficacy of montelukast in 6- to 24-month-old patients with asthma. Curr Med Res Opin 2005; 21: 971-979

[2] Knorr B, *et al.* Montelukast, a leukotriene receptor antagonist, for the treatment of persistent asthma in children aged 2 to 5 years. Pediatrics 2001; 108: E48

[3] Bisgaard H, *et al*. Montelukast reduces asthma exacerbations in 2- to 5-year-old children with intermittent asthma. Am J Respir Crit Care Med 2005; 171: 315-322

[4] Szefler SJ, *et al*. Comparative study of budesonide inhalation suspension and montelukast in young children with mild persistent asthma. J Allergy Clin Immunol 2007; 120: 1043-1050

Secondary efficacy endpoints were:
- the number of days without taking short-acting beta-2 agonists
- the percentage of those withdrawing from the study due to the asthma worsening
- the frequency of oral corticosteroid use
- the frequency of unforeseen consultations or hospital admissions
- the daily consumption of short-acting beta-2 agonists
- the frequency of exacerbations.

Results:
A total of 256 patients were included (a minimum of 150 children was foreseen in the protocol), of which 175 in the montelukast group and 81 in the placebo group.
The mean age of patients was 14.6 months; 32.8% were less than 1 year old. The majority of the children were given inhaled or nebulised corticosteroid treatment (50%) or cromones (10%) before inclusion. This population was given oral corticosteroid treatment for 7 days on average over the past year. About 37% had a personal history of allergies and 66% a family history of asthma. However, patients in the montelukast group had a more severe asthma, as 4% (compared to 0% in the placebo group) took oral corticosteroid treatment during the previous month and 11.4% during the previous year, compared to 7.4% in the placebo group.

No statistically significant difference was observed for any of the secondary endpoints studied. Furthermore, the study conditions (secondary efficacy endpoints and mixed severity) do not enable conclusions to be drawn as to the efficacy of montelukast in the population studied.

Placebo-controlled study of children aged 2 to 5 (PN072)
Randomised (2:1), double-blind study comparing montelukast 4 mg to placebo for 12 weeks in children aged 2 to 5 diagnosed with asthma. The primary objective of this study was to evaluate safety and the secondary objective was to evaluate efficacy.
Patients had to have had at least 3 asthma attacks over the year prior to inclusion, an overall asthma score of at least 1 (on a scale of 24) for at least 8 days during an initial 2-week period on placebo, and have taken short-acting beta-2 agonists for at least 8 days during this initial phase.
The treatments were administered in one intake in the evening. Treatments for the asthma attacks (short-acting beta-2 agonists) were authorised during the study and for 50% of the population, corticosteroids or cromones in inhaled or nebulised form; the latter had to be administered for at least 1 month before inclusion and maintained at a steady dose during the trial.

Secondary efficacy endpoints included:
- percentage of days with daytime symptoms (coughing, wheezing, respiratory problems and limited activity)
- percentage of days with a short-acting beta-2 agonist
- percentage of patients having had at least one asthma attack defined as a worsening of symptoms requiring oral corticosteroids, un unforeseen visit to the doctor's, A&E or hospital facility
- percentage of patients who took oral corticosteroids
- daytime asthma symptom score (scale of 0 to 5)
- nighttime asthma symptom score (scale of 0 to 4).

Results:
A total of 689 patients were included (a minimum of 510 children was foreseen in the protocol), of which 461 in the montelukast group and 228 in the placebo group.
The mean age of patients was 3.6 months; 45.5% were under 3 years old. The asthma had been progressing for 2.4 years on average, with symptoms occurring and use of short-acting

beta-2 agonists 6 days a week on average, during the initial placebo phase. On inclusion, 28% of children were given inhaled corticosteroids and 13% cromones. Almost 50% tested positive for allergies.

After 12 weeks' treatment, there was a significant difference between montelukast and placebo for all the aforementioned parameters except the percentage of patients who had at least one asthma attack (see table 1).

Table 1: Efficacy results after 12 weeks' treatment (study PN072)

Endpoints	**Montelukast**	**Placebo**	**Least squares mean of difference, $_{95\%}$CI**	**p**
% of days with daytime symptoms	59	64	- 5.57 [-9.91; 1.23]	0.012
% of days with short-acting β2 agonists	49	55	- 6.25 [-10.0; -2.43]	0.001
% of patients with at least one asthma attack	32	26	-	0.107
% of patients who took oral corticosteroids	19	28	-	0.008
Daytime symptom score Baseline score Change	 0.98 -0.37	 0.95 -0.26	 - 0.12 [-0.20; -0.04]	0.003
Nighttime symptom score: Baseline score Change	 1.18 -0.46	 1.20 -0.37	 - 0.11 [-0.21; -0.01]	0.026

Placebo-controlled study of children aged 2 to 5 with virally induced asthma attacks (PREVIA study)

Randomised, double-blind study comparing montelukast to placebo in the prevention of exacerbations, over 12 months, in children aged 2 to 5 with mild persistent asthma with exacerbations caused by acute viral infection.

The patients must not have had any symptom or took symptomatic treatment for attacks with short-acting beta-2 agonists for one week during the 3 months prior to the study.

Patients treated with montelukast were given a daily dose of 4 mg, except for patients over 5 years old (13%) who were given a 5 mg dose.

The primary endpoint was the number of exacerbations defined as:

- 3 consecutive days:
  - with daytime symptoms (cough, wheezing, respiratory problems) corresponding to a mean minimal daily score
  - and at least 2 daily intakes of beta-2 agonists or corticosteroids in oral or inhaled form for at least one day.
- or admission to hospital for asthma.

Secondary endpoints included:

- percentage of patients suffering from exacerbations
- time until first exacerbation
- percentage of days without asthma
- frequency of concomitant oral or inhaled corticosteroid treatments.

Results:

A total of 549 patients were included of which 278 in the montelukast group and 271 in the placebo group.

The mean age of patients was 44 months; 28% were under 3 years old. Most of the patients had had daytime asthma symptoms ≤ twice a week over the month prior to inclusion and 67% had not used oral corticosteroids over the year. Around 45% took inhaled corticosteroids over the previous 6 months.

After 12 months' treatment, the mean annual frequency of exacerbations was lower with montelukast than with the placebo: 1.60 compared to 2.34, i.e. a relative risk of 0.68; (95%CI = 0.56; 0.83] p ≤ 0.001).

The percentage of patients suffering from exacerbations and the median time until the first exacerbation were lower for patients treated with montelukast than with the placebo. However, montelukast was not different to the placebo for the percentage of symptom-free days (see table 2).

Table 2: Secondary endpoints concerning exacerbations (PREVIA study)

Endpoints	**Montelukast N = 278**	**Placebo N = 271**	**p**
Percentage of patients with at least one exacerbation	45%	56%	0.008
Median time until first exacerbation	206 days	147 days	0.024
Percentage of symptom-free days	75.8%	72.7%	0.059

Montelukast was able to reduce the use of inhaled corticosteroids (RR = 0.60; 95%CI = [0.38; 0.94]) but not oral corticosteroids (RR = 0.82; 95%CI = [0.54; 1.25]).

Study comparing with inhaled budesonide (Szefler study)

Randomised, open-label study comparing nebulised budesonide (PULMICORT) to montelukast over 12 months in children aged 2 to 8 years with mild persistent asthma or recurring bouts of wheezing.

Children under the age of 2 years were included; children aged 0 to 5 years made up 65% of the study population.

Patients were given either budesonide at a dose of 0.5 mg per day (in nebulised form) or montelukast at a dose of 4 or 5 mg according to age.

NB: in France, nebulised budesonide is indicated for severe persistent asthma.

The primary endpoint was the time until the first dose of another asthma treatment for mild to severe exacerbation.
Mild exacerbation was defined as the need to give patients an additional 0.5 mg of budesonide and at least 3 doses of short-acting beta-2 agonists over 4 out of 7 consecutive days, or waking at night due to symptoms at least 2 days out of 7.
Severe exacerbation was defined as the need to give patients an oral corticosteroid for 3 to 7 days and the use of 6 doses of short-acting beta-2 agonists over 24 hours, or 10 doses over 48 hours, or admission to hospital.

Efficacy was analysed on a modified intention-to-treat basis defined as those patients given the treatment at least once.

Results:
A total of 395 patients were included of which 197 in the montelukast group and 198 in the budesonide group. Fifty-two patients in the montelukast group and 63 in the budesonide group did not complete the study. Seven percent were lost to follow-up in each group and 2% discontinued treatment for adverse effects in the montelukast group and 1% in the budesonide group.

After 12 months' treatment, there was no significant difference between the nebulised budesonide group and the montelukast group in terms of time until the first dose of another asthma treatment. The Kaplan-Meier curve analysis showed a divergence between the 2 curves in favour of budesonide at the start of treatment with a peak at 12 weeks (statistically significant difference) to then converge at week 26.

3.2. Adverse effects

In clinical studies in children aged 6 months to 5 years and long-term extensions, the main treatment-related adverse effects were gastrointestinal problems (vomiting, diarrhoea). These adverse effects are similar to those observed in older children and adults.

SINGULAIR 4 mg is marketed in 74 countries in the chewable tablet form and in 48 countries in the granule form. The last PSUR covering the period from January 31, to July 30 2008 (i.e. 138,503 child patient-years for the chewable tablet form and 274,883 child patient-years for the granule form) showed no new signs of tolerance, compared to other SINGULAIR products.

3.3. Conclusion

Montelukast at a dose of 4 mg per day was compared to placebo in 2 randomised, double-blind safety studies involving patients with mild to moderate persistent asthma, one on children aged 6 months to 2 years and the other on children aged 2 to 5 years. Montelukast was given as a single agent or in addition to an inhaled corticosteroid treatment or a cromone, already introduced before the start of the trial. In both studies, the secondary objective was to evaluate efficacy.
The first study, which involved methodological biases, does not enable conclusions to be drawn as to the efficacy of montelukast in the 6 month to 2 year age category.
In children aged 2 to 5 years, after 12 weeks' treatment, there was a statistically significant difference in favour of montelukast compared to placebo for the following parameters: number of days with daytime symptoms, daytime symptom score, number of days with a short-acting beta-2 agonist, use of oral corticosteroids, nighttime symptoms. No statistically significant difference was observed in the percentage of patients having at least one asthma attack.

A randomised, double-blind placebo-controlled study was conducted on a specific population of children aged 2 to 5 with mild persistent asthma and asthma attacks caused by an acute viral infection. After 12 months' treatment, the mean annual frequency of exacerbations was lower with montelukast than with the placebo: 1.60 compared to 2.34, i.e. a relative risk of 0.68 (95%CI = 0.56; 0.83] p ≤ 0.001).

In a randomised, open-label study comparing nebulised budesonide (PULMICORT) to montelukast over 12 months in children aged 2 to 8 with mild persistent asthma or recurring bouts of wheezing, there was no significant difference in the time until inhaled or oral corticosteroid treatment was taken between the different treatment groups. Budesonide was more effective than montelukast for this endpoint at the start of treatment with maximum efficacy at 12 weeks (statistically significant difference).

Montelukast was tolerated well by children aged 6 months to 5 years, and adverse effects were essentially gastrointestinal, which is in line with the safety profile observed for older children and adults. The long-term safety profile for montelukast in the 1-year extension studies compared to placebo did not differ according to patient age.

Montelukast only proved to be effective in children with mild to moderate persistent asthma aged 2 to 5 years as a single agent or in addition to an inhaled corticosteroid or cromone. The effects observed can be described as moderate compared to the placebo. The data for children aged 6 months to 2 years involved methodological biases and does not enable conclusions to be drawn as to the efficacy of montelukast in this age category. The tolerance data for children aged 6 months to 5 years showed few adverse effects with montelukast and the latter were not severe.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Asthma is characterised by the development of a disability and a deterioration in quality of life. It can be life-threatening.

SINGULAIR 4 mg is part of the constitutional treatment for asthma patients aged 6 months to 5 years for the granule form and 2 to 5 years for the chewable tablet form.

Public health benefit:

The public health burden of asthma is substantial. Among the sub-population of patients likely to be given SINGULAIR in these indications, the burden is low, in view of the small number of patients concerned.

The improvement in the management of child asthma constitutes a public health need falling within the scope of public health priorities (Public Health Act 2004, paediatric products).

In spite of good safety and even if SINGULAIR holds the advantage of improving compliance in children, it is not expected to reduce asthma-related morbidity at population level.

Consequently, SINGULAIR is not expected to benefit public health for these indications.

The efficacy of montelukast was evaluated in children with mild to moderate persistent asthma not already treated or already treated with an inhaled corticosteroid or cromone.

The data for children aged 6 months to 2 years involved methodological biases and does not enable conclusions to be drawn as to the efficacy of montelukast in this age category.

In children aged 2 to 5 years, a moderate impact was observed on the number of days with daytime symptoms, daytime symptom score, number of days with a short-acting beta-2 agonist, use of oral corticosteroids, and nighttime symptoms. A decrease in the frequency of asthma exacerbations was observed only in children with asthma attacks induced by a viral infection.

No data is available on the use of montelukast as an alternative to low-dose inhaled corticosteroids in patients without a recent history of asthma attacks not observing their treatment or for exercise-induced asthma.

Montelukast is tolerated well by children aged 6 months to 5 years.

The efficacy/adverse effects ratio is high among children aged 2 to 5 years. This ratio cannot be assessed for those aged 6 months to 2 years.

These medicines are second-line constitutional treatments used:

- as a supplementary treatment to inhaled corticosteroids in children aged 2 to 5 years with mild to moderate persistent asthma inadequately controlled with inhaled corticosteroids and short-acting beta-2 agonists in the event of symptoms;
- as a single agent for children aged 2-5 years with mild persistent asthma, without a recent history of severe asthma attacks requiring treatment with oral corticosteroids with a demonstrated inability to observe low-dose inhaled corticosteroid treatment.

In the absence of demonstrated efficacy in children aged 6 months to 2 years, montelukast has no place in therapeutic use for the treatment of asthma in this age group.

In the preventive treatment of exercise-induced asthma in children aged 2 to 5 years, montelukast is a first-line treatment used as an alternative to short-acting beta-2 agonists.

In children under the age of 5 years, there are no alternative medicines for cases of inadequately controlled asthma despite good compliance to inhaled corticosteroids or otherwise and short-acting beta-2 agonists taken as needed.

The actual benefit of SINGULAIR 4 mg granules and chewable tablets is substantial in children aged 2 to 5 years for all indications.

The actual benefit of SINGULAIR 4 mg granules is not great enough in children aged 6 months to 2 years to be covered by national solidarity.

4.2. Improvement in actual benefit

SINGULAIR 4 mg chewable tablets and granules do not provide an improvement in actual benefit (IAB V) in the management of asthma patients aged 2 to 5 years.

4.3. Therapeutic use

Inhaled corticosteroids are the constitutional treatment for persistent asthma in children under the age of 5 years concomitant, in the event of symptoms, with a short-acting beta-2 agonist as needed. Long-acting beta-2 agonists are not recommended in this age group[5][6][7].

In mild to moderate persistent asthma in children aged 2 to 5 years, when the asthma is inadequately controlled with an inhaled corticosteroid, the addition of montelukast can be used as an alternative to doubling the inhaled corticosteroid dose.

[5] Global Initiative for Asthma ((2009 update for management of asthma in children under the age of 5)

[6] PRACTALL guidelines: The European Pediatric Asthma Group

[7] Management of asthma in children under the age of 36 months: French Paediatric allergology pneumology society guidelines in partnership with HAS (March 2009)

In mild persistent asthma in children aged 2 to 5 years, montelukast can be used as a single agent as an alternative to low-dose inhaled corticosteroids when the child has no recent history of severe asthma attacks requiring oral corticosteroids and if they have a demonstrated inability to observe inhaled corticosteroid treatment.

In the preventive treatment of exercise-induced asthma in children aged 2 to 5 years, montelukast is a first-line treatment used as an alternative to short-acting beta-2 agonists.

In children aged 6 months to 2 years, in the absence of demonstrated efficacy, montelukast is not recommended.

The response to treatment with montelukast must be evaluated after 2 to 4 weeks, and treatment should be discontinued when there is no response.

4.4. Target population

The target population of SINGULAIR 4 mg is comprised of children aged 2 to 5 years with:

- mild to moderate persistent asthma inadequately controlled with an inhaled corticosteroid treatment and a short-acting beta-2 agonist taken as needed;
- mild persistent asthma, without a recent history of severe asthma attacks requiring treatment with oral corticosteroids and with a demonstrated inability to observe inhaled corticosteroid treatment;
- exercise-induced asthma requiring preventive treatment.

According to IREDES[8] data (2008), the prevalence of asthma is 10.2% for the entire population and, for children aged 5 to 10 years, 10% of boys and 6% of girls. This survey did not specify the prevalence of asthma in children under the age of 5 years.
According to CREDES[9] data (1998), the prevalence of asthma was 5.8% for the entire population and, for children aged 5 to 10 years, 8.2% of boys and 5.0% of girls. The prevalence of asthma was also estimated as 6.5% for children under the age of 5 years (7.6% of boys and 5.2% of girls).
If we compare the 2006 and 1998 estimations, we can see an increase in prevalence of around 20%. If we consider that the prevalence of children under the age of 5 years has increased in a similar way, the current prevalence of asthma among children under the age of 5 years can be estimated as 7.8%.

Extrapolating this prevalence to the French population (INED 2008 data), the population of children aged 2 to 5 years with asthma can be estimated at about 248,600.

- **Mild to moderate persistent asthma inadequately controlled by inhaled corticosteroid treatment and a short-acting beta-2 agonist taken as needed**

In the CREDES survey (1998), the asthma was intermittent in 68.2% of cases and persistent in 31.8% of children aged 2 to 5 years. These values are in line with the data submitted by the company, from the Thales study conducted between 2006 and 2008, which led to the estimate that 27% of asthma cases were persistent (based on the prescribing of a constitutional treatment with 3 annual corticosteroid prescriptions). We can therefore consider that around 30% of children aged 2 to 5 years have persistent asthma, i.e. 74,600 children.

According to the IRDES survey (2008), in 60% of asthma patients, the asthma is inadequately controlled (based on GINA criteria). According to the stricter criteria of ANAES and Afssaps

[8] Afrite A, Allonier C, Com-Ruelle L, Le Guen N. L'asthme en France en 2006 : prévalence et contrôle des symptômes. IRDES questions d'Economie de la Santé. 2008;138:1-8.
[9] Com-Ruelle L, Crestin B, Dumesnil S. L'asthme en France selon les stades de sévérité. CREDES. 2000 N°1290

guidelines[10] (2004), the asthma is inadequately controlled in 83% of patients. In the Er'Asthme study[11] [12](2003) on 1,140 children aged 6 to 14 years, taking into account the Canadian criteria which were similar to HAS criteria, the asthma was inadequately controlled in 73% of children. Hence, it can be estimated that 60 to 83% of children aged 2 to 5 years suffer from inadequately controlled persistent asthma, i.e. 44,800 to 62,000 children.

Furthermore, the IRDES survey demonstrated that 50% of cases were inadequately controlled with a short-acting beta-2 agonist treatment taken as needed and 50% with a constitutional treatment: 38% with a constitutional treatment of intensity levels 2 and 3 and 12% with a constitutional treatment of intensity levels 4 and 5 (levels defined according to GINA guidelines). It can be considered that patients coming under the indication correspond to those treated with a constitutional treatment of intensity levels 2 and 3 and a share of those treated with a constitutional treatment of intensity levels 4 and 5 (making an approximation of an equal distribution between intensity levels 4 and 5).
In all, based on this data, for 44% of patients with persistent asthma, the asthma is inadequately controlled with a constitutional treatment corresponding to treatment for mild to moderate persistent asthma, i.e. 19,700 to 27,300 children aged 2 to 5 years.

- **Mild persistent asthma without a recent history of severe asthma attacks requiring treatment with oral corticosteroids and with a demonstrated inability to observe inhaled corticosteroid treatment**

According to data from the CREDES study (1998) and taking into account the increase of around 20% in prevalence between 1998 and 2006, mild persistent asthma represents 15% of all asthmas in children under 5, i.e. a population of 11,200.
There is no epidemiological data to estimate the population of children with mild persistent asthma with a history of severe asthma attacks.
Data in the literature[13][14] and from the Thales study estimate the lack of compliance with inhaled constitutional treatment as between 40 and 65%.
Hence, the population of patients with mild persistent asthma aged between 2 and 5 years not observing constitutional inhaled corticosteroid treatment can be estimated as between 4,500 and 7,300 children.

However, given the variability of the asthma over time and the need to adapt treatment to the level of control, this population is in all likelihood already included in the population of patients with mild to moderate persistent asthma inadequately controlled with inhaled corticosteroid treatment and a short-acting beta-2 agonist taken as needed.

- **Exercise-induced asthma requiring preventive treatment**

The epidemiological data available does not enable an estimate to be made of the population of children aged 2 to 5 years concerned by this indication.

To conclude, the target population of SINGULAIR 4 mg can be estimated as between 19,700 and 27,300 children aged 2 to 5 years.

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[10] Guidelines on medical care for adult and adolescent asthma patients. ANAES-Afssaps (2004) : www.has-sante.fr.
[11] Godard P, De Blic J, Huas D, Boucot I, Pribil C. ER'ASTHME: évaluation du contrôle de l'asthme chez 410 enfants âgés de 6 à 14 ans en médecine générale. Revue des Maladies Respiratoires, 2006;23(HS1):8
[12] De Blic J, Boucot I. Pribil C, Huas D, Godard P. Niveau de contrôle de l'asthme chez l'enfant en médecine générale en France: résultats de l'étude ER'ASTHME. Archives de Pédiatrie, 2007;14(9):1069-75
[13] Rand CS. Adherence to asthma therapy in preschool child. Allergy 2002;57(supl. 74):48-57
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4.5. Transparency Committee recommendations

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 for the indications and at the dosage stated in the MA.

The committee feels that it is regrettable that the efficacy of SINGULAIR 4 mg has not been demonstrated in the 0 to 2 year age group.

Packaging:
For treatments lasting one month, the Committee recommends harmonising the package size to 30 days' treatment and consequently 60-day packs for treatments lasting two months.

Reimbursement rate: 65%