



HAUTE AUTORITÉ DE SANTÉ

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TRANSPARENCY COMMITTEE

OPINION

16 June 2010

ARIDOL, inhalation powder, hard capsule
Box of 19 hard capsules with inhaler (CIP: 573 186-6)

Applicant: PRAXIS PHARMACEUTICAL FRANCE

Mannitol
ATC code: V04CX

List I
Medicinal product for hospital use only

Date of Marketing Authorisation: 19 August 2008 (mutual recognition)

Reason for request: Inclusion on the list of medicines approved for hospital use.

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Mannitol

1.2. Novel aspects

ARIDOL is the first product used to perform a bronchial hyperresponsiveness test to have the status of a medicinal product. It is the first test that requires the subject to inhale a powder. It is an indirect bronchial challenge test: inhalation of mannitol increases osmolarity within the airways, causing various bronchoconstriction mediators such as histamine, leukotrienes, prostaglandins, etc. to be released from the inflammatory cells in the airways. These mediators then act on the smooth muscle of the bronchi, causing them to contract.

1.3. Indication

“This medicinal product is for diagnostic use only.

ARIDOL is indicated for identifying bronchial hyperresponsiveness in subjects with a baseline FEV₁ of 70% or more of the predicted value.”

1.4. Dosage

“In adults

The ARIDOL capsules are supplied in kit form containing a sufficient number of capsules to complete one maximum dose challenge. The operator places the capsules one by one, according to a predetermined sequence, in the inhaler compartment and opens them by depressing the two buttons on the sides of the inhaler. This releases the mannitol powder from the capsule, and the patient can inhale it. Bronchial response to the cumulative effects of inhaled mannitol is measured by variations in FEV₁ shown by a spirometer. The first spirometer measurement is taken ‘blank’, before introducing mannitol, to determine the baseline FEV. This measurement is repeated to ensure that this baseline FEV₁ is reproducible.

For the actual test, the patient must be seated comfortably so that he or she can breathe in easily. A nose clip is applied so that the patient can only breathe through his or her mouth. The patient is asked to exhale completely. The inhaler is then given to the patient, who is asked to take a deep, rapid, controlled breath. A timer is started while the patient is inhaling, and the patient is asked to hold his or her breath for five seconds before exhaling. Sixty seconds later the patient is asked to breathe into the spirometer. Two successive FEV₁ measurements are taken, and the higher of the two readings is retained.

The operation starts with the capsule containing no mannitol to determine the baseline FEV₁. It is then repeated, with the patient inhaling the content of capsules containing 10 mg, 20 mg and 40 mg of mannitol in turn. Doses above 40 mg are obtained by asking the patient to inhale the content of several 40 mg capsules successively before taking a new spirometer reading.

The exercise can be continued until the patient has received a maximum cumulative dose of 635 mg of mannitol, as shown by the table below, but is stopped sooner if the patient produces a positive response to the test. A positive response is defined as:

- An FEV₁ reading that is 15% or more below the baseline FEV₁.
- An FEV₁ reading at a given dose of mannitol that is 10% or more below the reading obtained with the immediately preceding dose.

Mannitol dose steps for ARIDOL bronchial challenge tests			
Dose no.	Dose (mg)	Cumulative dose (mg)	Capsules per dose
1	0	0	1
2	5	5	1
3	10	15	1
4	20	35	1
5	40	75	1
6	80	155	2 x 40 mg
7	160	315	4 x 40 mg
8	160	475	4 x 40 mg
9	160	635	4 x 40 mg

Examples of positive test responses:

- FEV₁ fall following dose step 2: 3%
FEV₁ fall following dose step 3: 8%
FEV₁ fall following dose step 4: 16%
The total fall compared to the baseline FEV₁ is **16%** ($\geq 15\%$), and so the test is positive.

- FEV₁ fall following dose step 2: 3%
FEV₁ fall following dose step 3: 14%
The fall between two successive doses is **11%** ($\geq 10\%$), and so the test is positive.

Most patients recover spontaneously after a mannitol challenge test. However, those with a positive challenge or who experience serious breathing difficulties should receive a standard dose of a beta₂ agonist by inhalation to speed recovery. A dose of beta₂ agonist can also help speed recovery in some patients who tested negative. Following administration of a beta₂ agonist, FEV₁ usually returns to baseline within 10-20 minutes. As a precaution, patients should be monitored until their FEV₁ has returned to within 5% of baseline.

Children and adolescents (under 18)

The Aridol test should not be used in patients below 6 years of age due to their inability to provide reproducible spirometric measurements.

There is limited information on the use of ARIDOL in patients 6-18 years of age, and therefore ARIDOL is not recommended in this population.

Calculating PD15

The dose of mannitol required to cause a fall of 15% or more in FEV₁, known as PD15 ("Provocative dose to produce a 15% fall in FEV₁") is calculated by comparison with the baseline FEV₁ obtained with the capsule containing 0 g of mannitol."

1.5. Pharmacological properties

The ARIDOL test is an indirect bronchial challenge test: inhalation of mannitol increases osmolarity within the airways, causing various bronchoconstriction mediators such as histamine, leukotrienes, prostaglandins, etc. to be released from the inflammatory cells in the airways. These mediators then act on the smooth muscle of the bronchi, causing them to contract.

This test differs from direct tests which use pharmacological agents such as metacholine which cause bronchoconstriction by acting directly on specific bronchial muscle receptors.

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2010)

V	Various
V04	Diagnostic agents
V04C	Other diagnostic agents
V04CX	Other diagnostic agents

2.2. Medicines in the same therapeutic category

ARIDOL is the only medicinal product to have a diagnostic indication in the performance of bronchial hyperresponsiveness tests.

2.3. Medicines with a similar therapeutic aim

Other bronchial hyperresponsiveness tests exist, based on different principles:

- metacholine test
- eucapnic hyperventilation test
- vigorous exercise test
- AMP test (adenosine monophosphate)
- hypertonic saline test (solution containing 4.5% sodium chloride)

3 ANALYSIS OF AVAILABLE DATA

The company has submitted the following data in support of its request:

- six phase II studies comparing the mannitol test with other bronchial challenge tests
- one phase III study comparing the mannitol test with the hypertonic saline test.

3.1. Efficacy

Phase II studies

Mannitol test versus hypertonic saline test: Anderson (1997)¹

The study was carried out on 43 non-smoking asthmatic patients who were selected because they responded to the hypertonic saline test. Seven healthy subjects were also included as controls. The primary efficacy endpoint was the reduction in FEV₁ in response to bronchial challenge. The test was regarded as positive if this reduction was 15% of baseline FEV₁ (before challenge) for mannitol in powder form and 20% for the hypertonic saline.

42 of the 43 patients who responded positively to the hypertonic saline test responded positively to mannitol powder. None of the healthy non-asthmatic patients who were tested responded to the mannitol test before the maximum cumulative dose specified for the test (635 mg) was reached.

FEV₁ returned to the baseline level within 20 minutes in the case of patients given a bronchodilator, and to 95% of baseline after one hour in the case of patients not given a bronchodilator.

¹ Anderson et al. A new method for bronchial provocation testing in asthmatic subjects using a dry powder of mannitol. American Journal of Respiratory and Critical Care Medicine 1997;156:758-765.

Mannitol test versus hyperventilation test and/or vigorous exercise test: Brannan (1998)²

This study was conducted on 36 patients suffering from exercise-induced asthma aged 18 to 40 who were shown to have bronchial hyperresponsiveness by a vigorous exercise test (n = 23), a eucapnic hyperventilation test (n = 28) or by both tests (n = 15). All patients underwent the mannitol powder test until a 15% reduction in the baseline FEV₁ was achieved (or until they had taken a cumulative dose of 635 mg of mannitol).

The mannitol test was positive in 22 of the 23 patients who had responded positively to the vigorous exercise test and in the 28 patients who had responded positively to the eucapnic hyperventilation test.

Mannitol test versus metacholine test: Brannan (2000)³

This study was conducted on 24 asthmatic children who had experienced a 20% fall in the baseline FEV₁ when they inhaled a 16 mg/ml concentration of metacholine. Ten healthy children with no family history of asthma or major respiratory disease who had not responded to inhalation of metacholine were recruited as controls.

The aim of the study was to ascertain whether the children who responded to metacholine also responded to the mannitol test, to verify the repeatability of the test and to compare the time needed for both types of test to be carried out. Nine of the asthmatic children underwent the mannitol test twice.

21 of the 24 asthmatic children who had responded positively to inhalation of metacholine also responded to the mannitol test. The same response was obtained in the second test. None of the non-asthmatic children responded to the test.

The average times needed to perform the tests were 14 minutes for the mannitol test and 29 minutes with the metacholine test.

Specificity test for asthma-related bronchial hyperresponsiveness compared to the metacholine test: Porsbjerg (2007)⁴

This study was conducted on 16 subjects (aged 26 to 46) who responded to the metacholine test on inclusion but were not asthmatic. The subjects had the metacholine test and then, one week later, the mannitol test.

Fifteen of the sixteen subjects responded positively to the metacholine test but not to the mannitol test.

Mannitol test versus adenosine monophosphate (AMP) test: Currie (2003)⁵

This study was conducted on 15 patients with slight to moderate asthma whose pre-test FEV₁ was more than 60% of the predicted value.

In each test, the concentration of the product causing a 20% fall in baseline FEV₁ in the AMP test (PD₂₀) and a 15% fall in the mannitol test (PD₁₅) was determined.

Statistical analysis showed a strong correlation between the results of both tests. The Pearson coefficient between PD₂₀ and PD₁₅ was 0.80 (p<0.001). Between PD₁₅ and PD₂₀ it was 0.83 (p<0.001).

² Brannan JD et al. Responsiveness to mannitol in asthmatic subjects with exercise- and hyperventilation induced asthma. American Journal of Respiratory and Critical Care Medicine 1998;158:1120-1126

³ Brannan JD et al. Inhaled mannitol identifies methacholin-responsive children with active asthma. Pediatric Pulmology 2000;29:291-298

⁴ Porsbjerg C et al. Response to mannitol in asymptomatic subjects with airway hyperresponsiveness to methacholin. Clinical and Experimental Allergy 2007;37:22-28

⁵ Currie GP et al. Relationship between airway hyperresponsiveness to mannitol and adenosine monophosphate. Allergy 2003;58:762-766

Test for correlation between the response to the mannitol test and the degree of bronchial inflammation by comparison with the metacholine test: Porsbjerg (2007)⁶

This study was conducted on 53 non-smoking asthma patients (aged 26 to 56) who were not taking inhalational corticosteroids. The degree of bronchial activity was determined by an expectoration eosinophil count, the amount of NO exhaled, variations in peak exhalational flow (PEF) and replies to the Global Initiative for Asthma (GINA) questionnaire⁷. Patients' quality of life was assessed using the Juniper questionnaire which was specially designed for asthmatic patients.

34 of the 53 patients responded positively to the mannitol test, 34 to the metacholine test and 28 to both tests. The patients who responded had poorly controlled asthma and an impaired quality of life, while those who did not respond had fewer symptoms and a less severely impaired quality of life.

Inflammation factors were higher than normal in the patients who responded to both tests:

- NO concentrations in exhaled air were > 20 ppb in 83% of the patients who responded to the mannitol test and 88% of those who responded to the metacholine test;
- expectoration eosinophil levels were > 1% in 70% of the patients who responded to the mannitol test and 77% of those who responded to the metacholine test.

15% of unresponsive patients had an NO level of > 20 ppb, and none had an eosinophil level of > 1%.

The correlation between response to mannitol and eosinophil levels (PD15 vs. % of eosinophils: $r = -0.52$, $p < 0.05$) was closer than with metacholine (PD20 vs. % of eosinophils: $r = -0.28$, NS).

The correlation between response to mannitol and NO levels (PD15 vs. exhaled NO (ppb): $r = -0.63$, $p < 0.05$) was closer than with metacholine (PD20 vs. % of exhaled NO (ppb): $r = -0.43$, $p < 0.05$).

Phase III study

Mannitol versus hypertonic saline test: Brannan (2005)⁸

Randomised, single-blinded (operator-blinded) crossover study conducted on asthmatic and non-asthmatic subjects aged between 6 and 83 in order to assess the efficacy and tolerance of the mannitol test compared to the hypertonic saline test (4.5% concentration).

The asthmatic subjects had to have an FEV₁ level of > 70% of the predicted value and non-asthmatic subjects had to have an FEV₁ level of > 80% of the predicted value. None of the subjects could have an acute lower respiratory tract condition requiring medical attention, or any other acute or chronic pulmonary pathology, including pulmonary fibrosis, COPD, emphysema, tuberculosis, bronchiectasis, chronic bronchitis or cancer.

Before the tests, the subjects were required to:

- stop taking exercise and smoking for six hours,
- stop taking caffeine, short-acting bronchodilators, sodium cromoglycate, and nedocromil sodium for eight hours,
- stop taking inhalational corticosteroids alone or in combination with a long-acting bronchodilator and short-acting cholinergics for 12 hours,
- stop taking theophylline for 24 hours,
- stop taking long-acting anticholinergics and antihistamines for 72 hours, and
- stop taking antileukotrienes for four days.

⁶ Porsbjerg C et al. Relationship between airway responsiveness to mannitol and to methacholine and markers of airway inflammation, peak flow variability and quality of life in asthma patients. *Clinical and Experimental Allergy* 2007;38:43-50

⁷ Asthma severity score calculated using the GINA recommendations (1999) based on symptoms, FEV₁ and PEF.

⁸ Brannan JD et al. The safety and efficacy of inhaled dry powder mannitol as a bronchial provocation test for airway hyperresponsiveness: a phase 3 comparison study with hypertonic (4,5 %) saline. *Respiratory Research* 2005;6:144-155

Participants were advised not to change their dose of inhalational corticosteroids during the study.

The subjects were randomised as to the order in which they underwent the tests, which were performed at one-week intervals.

The operator who performed the first test was not aware of the asthmatic status of the subjects, and the operator who performed the second test was not aware of the asthmatic status of the subjects or of the result of the first test.

For the mannitol test, FEV₁ readings were taken 60 seconds after each dose of mannitol (5, 10, 20, 40, 80, 160, 160 and 160 mg). If the FEV₁ level had fallen by 10%, the same dose was repeated. The test was continued until a 15% fall in FEV₁ occurred or a cumulative dose of 635 mg had been given.

For the hypertonic saline test, subjects were exposed to a spray mist of a 4.5% solution for 30 seconds, 1 minute, 2 minutes, 4 minutes and 8 minutes. The flow rate of the ultrasonic nebuliser had to be at least 1.5 ml/min. FEV₁ readings were taken 60 seconds after each exposure. If the FEV₁ level had fallen by 10%, the same length of exposure was repeated. The test was continued until a 15% fall in FEV₁ had occurred.

Endpoints: sensitivity and specificity of the mannitol test compared to the saline test.

Sensitivity: likelihood of a positive mannitol test result coinciding with a positive saline test result, i.e. the proportion of subjects testing positive for mannitol compared to the total number of subjects testing for hypertonic saline.

Specificity: likelihood of a negative mannitol test result coinciding with a negative saline test result, i.e. the proportion of subjects testing negative for mannitol compared to the total number of subjects testing negative for hypertonic saline.

Results:

83.2% (n = 487) of the 592 subjects included and completing the study (out of 654 initially recruited) were asthmatic and 17.7% (n = 105) were non-asthmatic.

Of the 378 adult asthmatics, 50.5% had mild asthma, 40% had moderate asthma and 9.5% had severe asthma⁹.

Of the 109 asthmatic children, 22.0% had symptoms classified as non-frequent, 17.4% had frequent symptoms and 60.6% had persistent symptoms.

78.4% of the subjects diagnosed as asthmatic on entry into the study were taking at least one asthma drug: 27.7% were taking an inhalational corticosteroid in isolation, 38.5% were taking an inhalational corticosteroid in combination with a long-acting bronchodilator, 15.6% were taking an inhalational corticosteroid in combination with a short-acting bronchodilator and 3 were taking only a long-acting bronchodilator. Only 1.7% was taking an antileukotriene, 4.6% an anticholinergic agent and 2.2% sodium cromoglycate.

The test results are presented in table 1.

Sensitivity and specificity tests:

The sensitivity and specificity of the mannitol test compared with clinical examination were 59.8% and 94.5%.

159 (81.1%) of the 196 subjects producing a negative result in the mannitol test had been taking an inhalational corticosteroid before the first test. 204 (70.1%) of the 291 subjects who produced a positive result in the mannitol test had been taking an inhalational corticosteroid before the first test.

An exploratory analysis was carried out to rule out mannitol-negative subjects who had been taking an inhalational corticosteroid before the first test. This is because as mannitol works by triggering the release of inflammation mediators by inflammatory cells, treatment with

⁹ National Asthma Council of Australia Management Handbook Guidelines

inhalational corticosteroids before the test can interfere with the action of mannitol. Under these conditions, sensitivity was 88.7% and specificity was 95%.

The sensitivity and specificity of the saline test compared to clinical examination were 65.1% and 95.2%.

The sensitivity and specificity of the mannitol test compared with the saline test were 80.7% and 86.7%.

Table 1: test results

Parameters	Mannitol test	Hypertonic saline test
Responders: n (%)	296 (50.0)	322 (54.4)
Average dose administered to responders	239.0 ± 135 mg	12.9 ± 11.3 ml
Average dose administered to non-responders	635.0 ± 0.9 mg	32.4 ± 6.3 ml
PD ₁₅	112.20 mg	5.01 ml
Mean of the maximum FEV ₁ reduction	21.0 ± 5.7 %	21.3 ± 5.9 %
Correlation between response and maximum FEV ₁ reduction (r)	0.62 (p < 0.001)	0.62 (p < 0.001)

3.2. Supplementary data

A study published in 2009 by Sverrild et al.¹⁰ assessed the diagnostic efficacy of the mannitol test on a population of young adults drawn at random from the Danish national population register.

Subjects drawn at random were given a 20-point questionnaire derived from the screening programme run by the American College of Allergy, Asthma and Immunology, plus questions on smoking habits.

During a clinical examination, measurements were taken of all participants' exhaled NO fraction and respiratory function. They also underwent a skin prick test and a mannitol test, and the reversibility of bronchoconstriction in response to beta-2 agonists was assessed. Participants who were on anti-asthma treatment (short- or long-acting inhalational beta-2 agonists, anti-leukotrienes, oral bronchodilators and inhalational corticosteroids) were required to stop taking them before the clinical examination. They were asked to complete an asthma symptoms questionnaire based on the GINA recommendations.

The mannitol test was carried out in accordance with the protocol which had been validated by the marketing authorisation. It was stopped once a fall of at least 15% in baseline FEV₁ had been obtained or once the subject had received a maximum dose of 635 mg.

Sensitivity, specificity, positive predictive value and negative predictive value were calculated for PD₁₅.

Results:

978 of the 1,000 individuals drawn at random were contactable, 448 (45.8%) responded by returning the questionnaire and 238 (24.3%) agreed to take part in the study.

The average age of the participants was 18. 21.8% were asthmatic, 41.6% were atopic, 46.2% had rhinitis and 21.8% were smokers (smoking more than one cigarette a day). The only difference between the subjects who took part in the study and those who only took part in the screening phase was the gender split.

The average baseline FEV₁ was 97% of the predicted value.

The test results according to asthma status are presented in table 2.

¹⁰ Sverrild A, Porsbjerg C et al. Diagnostic properties of inhaled mannitol in the diagnosis of asthma : a population study. J Allergy Clin Immunol 2009;124(5):928-932

Table 2: mannitol test results

	Diagnosed with asthma N =51	Not asthmatic N = 187
15% reduction in FEV₁		
Positive test (%)	30 (58.8)	3 (1.6)
Negative test (%)	21 (41.2)	184 (98.4)
PD15 (mg)		
Mean	250.2 ± 203.9	430.6 ± 29.9
Median	197.3	436.5
% reduction in FEV₁		
Mean	14.7 ± 7.3	3.8 ± 4.1
Median	15.9	3.1

Specificity was 98.4% (95%CI = [96.2; 99.4]) and sensitivity was 58.8% (95%CI = [50.7; 62.6]).

Among the 33 participants positive to the test, 30 had been diagnosed with asthma, giving a positive predictive value of 90.9% (95%CI = [78.4; 96.8]).

Among the 205 participants negative to the test, 184 had been diagnosed as not having asthma, giving a negative predictive value of 89.8 % (95%CI = [87.7; 90.7]).

3.3. Adverse effects

In the phase III study comparing the mannitol test with the hypertonic saline test, the 646 subjects who made up the intention-to-treat population were included in the tolerance analysis. 627 of them had had the mannitol test and 636 had had the hypertonic saline test. Adverse events were recorded on the day of the test and for seven days after the test.

The adverse event most frequently observed after the mannitol test was headache ($\geq 1/10$).

The other frequent adverse events ($\geq 1/100$ to $<1/10$) were: pharyngeal pain, cough (requiring suspension of the test), rhinorrhoea, throat irritation, rhinopharyngitis, upper respiratory tract infection, aggravation of asthma, dyspnoea, nausea, upper abdominal pain, diarrhoea, vomiting, fatigue, chest tightness and spinal pain.

A similar adverse event pattern was observed with the hypertonic saline test.

No serious adverse events occurred.

The drug tolerance data obtained after ARIDOL was placed on the market (28 April 2008 to 20 April 2009) did not bring to light any additional adverse effects other than those referred to in the SPC.

3.4. Conclusion

The six comparative phase II studies carried out on small cohorts show that the mannitol test carried out on adults or children diagnosed with asthma produces bronchial hyperresponsiveness results that are consistent with the results of other tests available (metacholine, hypertonic saline, AMP, eucapnic hyperventilation, vigorous exercise). These studies also showed good reproducibility of the results, a good correlation with the degree of bronchial inflammation and specificity for bronchial hyperresponsiveness associated with asthma. One study found that on average the mannitol was faster to perform than the metacholine test (14 minutes vs. 29 minutes). Subjects receiving a short-acting bronchodilator regained baseline FEV₁ levels after the mannitol test more quickly than those who were not (20 minutes versus one hour without a bronchodilator).

The randomised, single-blinded (operator-blinded) crossover phase III study comparing the mannitol test with the hypertonic saline test in 592 asthmatic and non-asthmatic adults and children found the sensitivity and specificity of the mannitol test compared to the saline test to be 80.7% and 86.7%. The sensitivity and specificity of the mannitol test compared with clinical examination were 59.8% and 94.5%. An exploratory analysis was carried out to exclude mannitol-negative subjects who had been taking an inhalational corticosteroid prior to the first test (as mannitol triggers the release of inflammation mediators by inflammatory

cells). Under these conditions, sensitivity and specificity compared to clinical examination were 88.7% and 95%.

In this study, the adverse events pattern during the tests and for seven days after the tests were similar in the case of both the mannitol test and the hypertonic saline test: primarily headache, nausea, pharyngeal pain and cough requiring the test to be suspended.

A study published in 2009 by Sverrild et al. confirmed the diagnostic efficacy of the mannitol test on a population of 238 young adults aged 18 to 24 drawn at random from the Danish national population register. The asthma status of each participant was determined during a clinical examination before the test was performed. 51 of the 238 participants were found to be asthmatic. They were required to stop taking their asthma treatment before the test. The sensitivity of the test was 58.8% (95%CI = [50.7; 62.6]) and its specificity was 98.4% (95%CI = [96.2; 99.4]). The positive predictive value was 90.9 % (95%CI = [78.4; 96.8]) the negative predictive value was 89.8% (95%CI = [87.7; 90.7]).

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Bronchial hyperresponsiveness is a tendency in the smooth muscles of the bronchial tree to contract more intensely in response to a given stimulus than is the case with normal individuals. It occurs in almost all asthma patients, and is often associated with allergic rhinitis. It can also be associated with non-respiratory pathologies (cardiac insufficiency, digestive inflammatory diseases, gastro-oesophageal reflux, and systemic conditions). Bronchial hyperresponsiveness causes symptoms which appear trivial: dyspnoea, possibly wheezing, and an irritating cough.

This medicinal product is for diagnostic use.

Public health benefit:

ARIDOL is used to diagnose bronchial hyperresponsiveness. This hyperresponsiveness can be associated with asthma. Asthma is diagnosed by a clinical test (spirometry). Bronchial hyperresponsiveness tests are useful only in cases where a diagnosis cannot be clearly established. The burden is therefore minor at best.

Improving the diagnosis of asthma is not a public health need.

As other bronchial hyperresponsiveness tests exist, and in view of the data available, ARIDOL is not likely to lead to any improvement in the diagnosis of asthma.

Consequently, ARIDOL is not expected to have an impact on public health.

The efficacy/adverse effects ratio is high. The data supplied relates only to patients with asthma.

Evidence of bronchial hyperresponsiveness via a challenge test can be useful in cases where it is difficult to clearly establish a diagnosis of asthma.

There are alternatives that do not have medicinal product status, in particular the metacholine test.

In the absence of precise data on the population covered by the indication, the actual benefit of ARIDOL is moderate.

4.2. Improvement in actual benefit (IAB)

ARIDOL powder for inhalation in capsules provides a minor improvement in actual benefit (IAB IV) in the diagnostic strategy of bronchial hyperresponsiveness.

4.3. Therapeutic use

Bronchial hyperresponsiveness is associated with respiratory conditions such as asthma and rhinitis, but also with other conditions.

Asthma is diagnosed by a clinical examination and spirometry. Though no specific guidelines exist, a bronchial hyperresponsiveness challenge test can be useful in diagnosing unclear cases.

In allergic rhinitis, the test can reveal associated bronchial hyperresponsiveness that can underlie or develop into asthma.

There are different types of bronchial hyperresponsiveness test: the metacholine test, which is the most commonly used procedure, the hypertonic saline test, the AMP test, the vigorous exercise test and the eucapnic hyperventilation test. ARIDOL is an additional bronchial hyperresponsiveness test that differs from the other tests in respect of its status as a medicinal product and the fact that it involves inhalational administration of mannitol powder supplied in kit form requiring no additional equipment.

4.4. Target population

It is difficult to estimate the population of patients requiring a bronchial hyperresponsiveness challenge test as there is no epidemiological data concerning these patients and as the procedure does not have to be recorded in the PMSI medical information database.

The company estimates the target population for ARIDOL as between 12,000 and 20,000 patients.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines approved for use by hospitals and various public services in the indications and at the dosages in the Marketing Authorisation.