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The economic burden of severe asthma in children: a comprehensive study

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ABSTRACT

Objective: The economic burden of severe asthma (SA) in children is poorly described. We aimed to determine the healthcare costs of SA in children for the French national health insurance (NHI).

Methods: Children (6–18 years of age) with physician-confirmed diagnoses of SA or non-SA (NSA) were identified. Direct and indirect expenditures related to asthma and associated comorbidities in the previous six months were determined, based on a physician-guided parental questionnaire and confirmed by medical records. The costs for the French NHI were assessed per child over a six month period.

Results: Data from 74 children, including 48 with SA (22 requiring omalizumab) and 26 with NSA, were analyzed. The global cost of SA was €3,982 per child over a six-month period, including €3,821 direct costs and €161.9 indirect costs. The global cost was €6,716 (4,220) for those requiring omalizumab vs. €1,669 (3,108) for those who did not ($p < 0.01$). For children with SA, 65% of direct costs were attributed to medication. Among those on omalizumab, such treatment accounted for 93% of medication costs. The global cost was 10 times higher for children with SA than those with NSA (€3,982 (4,422) vs. €363.2 (352.6), $p < 0.01$), and 20 times higher for children with SA on omalizumab than those with NSA ($p < 0.01$).

Conclusion: The economic burden of SA in children for the French NHI is substantial and mainly driven by the most severe children requiring biologics.

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Introduction

Asthma is the most common chronic disease among children, affecting 235 million children worldwide (1). In France, the 2012–2013 prevalence of wheezing in the prior 12 months was 11.8% for preschoolers (mean age 5.7 years) (2). In 2008–2009, the cumulative prevalence of asthma was 14% in the 5th year of elementary school and 16% in the 4th year of secondary school (3).

In children, asthma control is generally achieved with low to moderate doses of inhaled corticosteroids (ICS). However, approximately 5% of children suffering from severe asthma (SA) remain symptomatic despite high doses of ICS, other controllers and the control of aggravating factors (4). The annual cost of SA in children was estimated to range between 1,840 and 7,846 US dollars (\$) (5–8). SA may account for approximately half of total pediatric asthma healthcare

costs (9). Most studies assessing asthma-related healthcare costs have included both children and adults, with varying levels of asthma severity, but very little child-specific data are available (10–14). Patients are often identified indirectly by a top-down approach using algorithms or by parental declaration. Thus the severity of asthma may be misestimated. Finally, the data analyzed vary among studies, with biologics and rehabilitation being rarely considered. In one study, the costs of asthma in children were assessed by a bottom-up approach, after children were identified by physicians using questionnaire-guided interviews and medical records, and the severity of asthma was assessed based on the Global Initiative for Asthma (GINA) guidelines (15). However, only 10 of the 618 children had SA (15).

In 2010, the estimated cost of controlled asthma was €85.40 euros/patient/trimester vs. €537.90 for

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uncontrolled asthma for adult patients recruited by general practitioners (16). Annual asthma-related costs were estimated to be 8,222 euros (€) for adults with SA from the French COBRA cohort (17) and annual direct costs \$9,227 per year in another French cohort (18). However, data on pediatric SA costs in France are still lacking. In addition, children with SA form a heterogeneous group. Some children with SA have a particularly severe phenotype, and remain symptomatic despite the optimal use of high doses of ICS and other controllers, the control of environment and the treatment of aggravating factors (19,20). In this group of children, biologics such as anti-IgE treatment are indicated to control asthma symptoms. Costs may differ among children with SA who are receiving, or not, anti-IgE treatment. However, such distinction is rarely taken into consideration when analyzing costs of SA. We aimed to determine the healthcare costs of SA for the French national health insurance (NHI) in a well-defined population of children with physician-confirmed diagnoses of SA or NSA, based on an individual evaluation of costs in the previous six months. We then compared healthcare costs in children with SA with and without bioterapy, and between children with SA and non-SA.

Materials and methods

Subjects

Children (6–18 years of age) with asthma, regularly followed in the department of Pediatric Pulmonology of Necker Hospital were recruited during outpatient visits between May 1, 2018 and October 30, 2018. The diagnosis of asthma was confirmed by a specialist physician and asthma severity was defined based on the GINA guidelines (21). Children were seen 2–3 times per year. At each visit, symptoms, comorbidities, adherence to treatment, inhalation methods were recorded. SA was defined as asthma requiring step 4 or 5 of treatment of the GINA classification and NSA as requiring steps 1 to 3 (21). Some of the children with persistent symptoms and/or airway limitation on spirometry despite high doses of ICS and other controllers, good adherence and inhalation technique, underwent investigations, including bronchial endoscopy, and have been previously described (22–24). Children diagnosed with conditions other than asthma were excluded. Parents were informed and accepted to participate in the study, the local ethical committee confirmed that Institutional Review Board approval was not required.

Evaluation of costs

A physician-guided questionnaire was performed with parents to assess individual expenditures related to asthma and associated comorbidities in the previous six months (between November 1, 2017 and April 30, 2018). Analysis of the medical records confirmed the parental claims. All economic variables were quantified in euros (€). Costs were expressed per child, over a six-month period.

Direct costs

Medications

Medications and medical devices analyzed are described in details in the [supplemental information](#). The unit prices of medications and their reimbursement rate by the NHI are available in the VIDAL Drug Information System (25). The unit cost of devices for the NHI are available in the List of Reimbursable Products and Services (*Liste des Produits et Prestations Remboursables, LPPR*) with LPPR codes 1128423, 1172772, 101C0313 and ACL codes 5402513, 7033089, 4650491 for inhaler, peak flow, and nebulizer with child mask, respectively (26) (see [supplemental information](#) for full details).

Medical visits

For each patient, the number of medical visits for asthma, asthma-related diseases or comorbidities were determined by parental report and confirmed through medical record. The cost of consultations for the NHI was obtained by multiplying the cost of one consultation (27) by the number of consultations (see [supplemental information](#) for full details).

Emergency department (ED) visits

For each patient, the number of ED visits for acute asthma was determined. The cost of an ED visit was €655 regardless of the amount of individual care required (see [supplemental information](#) for full details).

Hospitalizations/admissions

The number of admissions in pediatric or pediatric pulmonology departments for acute asthma or asthma work-up, and the number of admissions in a day care unit (DCU) for asthma or asthma-related conditions were determined (see [supplemental information](#) for full details).

Rehabilitation

Some patients with SA were admitted to rehabilitation center to benefit from favorable climatic conditions. Total costs of these stays for the NHI were provided by the financial department of the center.

Outpatient clinical and laboratory tests

The number of asthma-related tests and procedures performed were determined for each patient (see [supplemental information](#) for full details).

The cost for the NHI of blood drawing by direct intravenous puncture, performed in private settings, was based on the general nomenclature of professional acts (*la Nomenclature Générale des Actes Professionnels*, NGAP) provided by the NHI. The corresponding code was AMI 1.5, and the cost was €4.73 (28) (see [supplemental information](#) for full details).

Indirect costs

Parental lost working days and lost school days were determined by parental report. The cost related to parental lost working days were calculated by multiplying the number of lost days by the daily cost (based on a mean net salary of €2,250 per month, corresponding to €74 per day, according to data published by the National Institute of Statistics and Economic Studies in France). The base year for all cost calculations was 2015 (29). School loss due to asthma was expressed in days.

Global costs

Global costs were obtained by the addition of direct and indirect costs.

Statistical analysis

Data are expressed as the mean (SD) or n (%). Differences between groups were assessed using the Mann-Whitney test. A p values < 0.05 was considered to be significant. Data were analyzed using GraphPad Prism version 5.03 (GraphPad Software, Inc., San Diego, CA, USA).

Results

Subjects

Data from 74 children (12.6 y (3.2)) with physician-confirmed asthma were analyzed, including 48 with SA (22 requiring omalizumab) and 26 with NSA. The

general characteristics of the children are summarized in [Table 1](#) and [Supplemental Table 1](#) (see [supplemental information](#) for more details).

Direct costs

The individual direct costs for the NHI based on asthma severity are shown in [Tables 2](#) and [3](#), and [Supplemental Table 2](#). The individual direct costs for children with SA were €3,821 (4,350). For children requiring omalizumab it was €6,531 (4,101) and for children not taking omalizumab it was €1,527 (3,084) ($p < 0.01$). The individual direct costs increased from children with NSA to children with SA not taking omalizumab to those taking omalizumab (€297.7 (328.2) vs. €1,527 (3,084) vs. €6,531 (4,101), $p < 0.01$) (see [Supplemental Table 2](#)). When omalizumab was not taken into consideration, we observed the same trend within these three groups (€297.7 (328.2) vs. €1,527 (3,084) vs. €1,787 (2,174), $p < 0.01$). The direct costs were approximately 13 times higher for children with SA than for those with NSA (€3,821 (4,350) vs. €297.7 (328.2), $p < 0.01$).

Medications

Medication costs are detailed in [Table 4](#), [Supplemental Table 3](#) and [Supplemental Figure 1](#) (see [Supplemental Table 4](#) for details on purchased medications). When all children with SA were considered together, medication costs accounted for 65% of direct costs (€2,492 (3,516)), and omalizumab contributed to 87.2% of medication costs (€2,175 (3,459)). In children requiring omalizumab, this treatment accounted for 93% (€4,745 (3742)) of medication costs. The costs of the other medications did not differ between children with SA taking omalizumab and those who were not (€1,527 (3,084) vs. €1,787 (2,174), $p = 0.13$). Medication costs were approximately 20 times higher for children with SA than those with NSA (€2,492 (3,516) vs. €126.9 (154.4), $p < 0.01$). Medication costs remained 2.5 times higher for children with SA than those with NSA (€317.3 (201.5) vs. €126.9 (154.4), $p < 0.01$) when the cost of omalizumab was not included.

Medical visits

Physician visit costs accounted for 3% of direct costs for children with SA, and were higher for children with SA than those with NSA (€115.8 (96.46) vs. €43.5 (34.99), $p < 0.01$) (see [supplemental information](#) for more details).

Table 1. General characteristics of the population according to asthma severity.

Characteristics	Total population	SA	NSA	P
GINA step				
Step 1	6 (8.1%)	0	6 (23.1%)	
Step 2	4 (5.4%)	0	4 (15.4%)	
Step 3	16 (21.6%)	0	16 (61.5%)	
Step 4	26 (35.1%)	26 (54.2%)	0	
Step 5	22 (29.7%)	22 (45.8%)	0	
Gender				
Male/female	39/35	30/18	9/17	0.02
Age (years)	12.95 [10.08 – 15.33]	13.4 [10.73 – 16.18]	12.05 [8.525 – 14.00]	0.06
< 12	30 (40.5%)	17 (35.4%)	12 (46.2%)	
≥ 12	44 (59.5%)	31 (64.6%)	14 (53.8%)	0.37
BMI (kg/m ²)	19.25 [16.49 – 22.06]	19.37 [17.14 – 21.91]	18.35[15.27 – 22.25]	0.30
Atopy	53/74 (71.6%)	39 (81.3%)	14 (53.8%)	0.01
Comorbid diseases				
Atopic dermatitis	20 (27%)	15 (31.2%)	5 (19.2%)	0.27
Food allergy	11 (14.8%)	8 (16.6%)	3 (11.5%)	0.56
Allergic rhinitis+/-conjunctivitis	50 (67.5%)	37 (77%)	13 (50%)	0.02
Nasal polyps	2 (2.7%)	1 (2.1%)	1 (3.8%)	0.67
Sinusitis	4 (5.4%)	3 (6.3%)	1 (3.8%)	0.68
Gastroesophageal reflux disease	17 (22.9%)	14 (29.1%)	3 (11.5%)	0.09
Obstructive sleep apnea syndrome	2 (2.7%)	1 (2.1%)	1 (6.2%)	0.67
Influenza vaccination	30 (40.5%)	21 (43.7%)	9 (34.6%)	0.45
Treatments				
ICS, n (%)	68 (91.8%)	48 (100%)	20 (76.9%)	<0.01
Dose of ICS(μg/d flu eq)	500 [200-500]	500 [500-500]	200 [75-200]	<0.01
LABA, n (%)	58 (78.3%)	42 (87.5%)	16 (61.5%)	0.01
Nebulization for maintenance, n (%)	7 (9.4%)	7 (14.6%)	0	0.04
Leukotriene antagonists, n(%)	28 (33.7%)	26 (54.1%)	2 (7.7%)	<0.01
Long term antibiotic treatment, n (%)	3 (4.1%)	3 (6.3%)	0	0.20
Anti-Ig E, n (%)	22 (29.7%)	22 (45.8%)	0	<0.01
Allergen Immunotherapy, n (%)	5 (6.7%)	1 (2.1%)	4 (15.4%)	0.03
Rehabilitation	2 (2.7%)	2 (4.2%)	0	0.30
Patients with outpatient clinical and laboratory tests, n (%)				
Spirometry	50 (67.5%)	35 (72.9%)	15 (57.6%)	0.19
At hospital	49 (66.2%)	35 (72.9%)	14 (53.8%)	0.10
In ambulatory	3 (4.1%)	1 (2.1%)	2 (7.7%)	0.25
skin test for allergy	19 (25.7%)	12 (25%)	7 (26.9%)	0.86
blood test for allergy-specific IgE	16 (21.6%)	15 (31.2%)	1 (3.8%)	<0.01
chest X-ray	6 (8.1%)	6 (12.5%)	0	0.06
ENT endoscopy	4 (5.4%)	4 (8.4%)	0	0.14
pHmetry	2 (2.7%)	2 (4.2%)	0	0.30
Emergency department visit	12 (16.2%)	11 (22.9%)	1 (3.8%)	0.04
Emergency department visit per patient	0.16	0.23	0.04	
Day Care Unit admission	3 (4.1%)	3 (6.3%)	0	0.20
Hospitalization	5 (6.7%)	4 (8.4%)	1 (3.8%)	0.47
in emergency unit	3 (4.1%)	2 (4.2%)	1 (3.8%)	0.96
in pulmonology unit	2 (2.7%)	2 (4.2%)	0	0.30
Urgent (unscheduled) physician visit in ambulatory	23 (31.1%)	21 (43.7%)	2 (7.7%)	<0.01
Scheduled physician visit				
Hospital outpatient visit				
To pulmonologist/allergist	60 (81.1%)	43 (89.6%)	17 (65.4%)	0.01
To ENT	4 (5.4%)	4 (8.4%)	0	0.13
To dermatologist	3 (4.1%)	2 (4.2%)	1 (3.8%)	0.93
To ophthalmologist	1 (1.4%)	1 (2.1%)	0	0.47
Ambulatory visit				
To general practitioner	9 (12.2%)	6 (12.5%)	3 (11.5%)	0.91
To pediatrician	4 (5.4%)	4 (8.4%)	0	0.14
To pulmonologist	4 (5.4%)	4 (8.4%)	0	0.14
To allergist	4 (5.4%)	1 (2.1%)	3 (11.5%)	0.09
To ENT specialist	8 (10.8%)	5 (10.4%)	3 (11.5%)	0.89
To ophthalmologist	2 (2.7%)	1 (2.1%)	1 (3.8%)	0.67

Data are expressed as the median [25% -75%] or n (%).

SA : severe asthma , NSA : non-severe asthma , BMI : body mass index, ICS : inhaled corticosteroids, μg/d flu eq : ug/day in fluticasone equivalent, LABA: long-acting beta-2 agonist, ENT : ear nose throat.

ED visits

ED visits accounted for 14% of direct costs for children with SA. The costs of ED visits were higher for children taking omalizumab than those who were not

(€952.7 (1839) vs. €176.3 (656.5), $p = 0.035$). For children with SA, ED visits accounted for 13.3% of global costs; they accounted for 14.1% of global costs for children taking omalizumab and decreased to 10.5%

Table 2. Estimated costs (€) of asthma according to asthma severity during the six-month study period.

	SA (n = 48)			NSA (n = 26)			p*
	Mean (SD)	Median [IQR]	95% CI	Mean (SD)	Median [IQR]	95% CI	
Direct costs							
Medications	2492 (3516)	505.4 [216.7-3634]	1471; 3513	126.9 (154.4)	93.39 [25.26-163.1]	64.57; 189.3	<0.01
Drugs	303.5 (191.3)	264 [176.7-356]	247.9; 359	91.20 (81.14)	80.16 [19.04-136.4]	58.43; 124	<0.01
Anti-Ig E	2175 (3459)	0 [0-3353]	1170; 3179	0 (0)	0 [0-0]	0; 0	<0.01
Immunotherapy	9.357 (64.83)	0 [0-0]	-9.467; 28.18	32.23 (105.3)	0 [0-0]	-10.32; 74.78	0.04
Influenza vaccination	4.423 (5.068)	0 [0-10.11]	2.951; 5.895	3.5 (4.905)	0 [0-10.11]	1.518; 5.481	0.45
Medical devices ^a	47.83 (85.62)	0 [0-64.82]	22.97; 72.69	2.04 (3.798)	0 [0-2.21]	0.5058; 3.574	0.02
Urgent (unscheduled) physician visit in ambulatory	36.46 (68.02)	0 [0-68.75]	16.71; 56.21	1.923 (6.794)	0 [0-0]	-0.8209; 4.667	<0.01
Scheduled physician visits	79.33 (56.09)	72 [28-112]	63.05; 95.62	41.58 (33.71)	28 [27.25-59.75]	27.96; 55.19	<0.01
Hospital outpatient visits	55.25 (41.73)	42 [28-84]	43.13; 67.37	25.77 (27.99)	28 [0-28]	14.46; 37.07	<0.01
To pulmonologist/allergist	50.58 (39.31)	28 [28-69]	39.17; 62	24.69 (24.32)	28 [0-69]	14.87; 34.51	<0.01
To another specialist	4.667 (14.54)	0 [0-0]	0.4459; 8.887	1.077 (5.491)	0 [0-0]	-1.141; 3.295	0.32
Ambulatory visits	24.08 (40.57)	0 [0-48]	12.3; 35.86	15.81 (23.51)	0 [0-48]	6.313; 25.3	0.73
To general practitioner	7.813 (26.38)	0 [0-0]	0.1539; 15.47	3.846 (11.6)	0 [0-0]	-0.8402; 8.532	0.87
To pediatrician	4.792 (18.95)	0 [0-0]	-0.7119; 10.3	0 (0)	0 [0-0]	0; 0	0.14
To another specialist	11.48 (24.66)	0 [0-0]	4.32; 18.64	11.96 (22.66)	0 [0-12]	2.808; 21.12	0.81
Outpatient Clinical and Laboratory tests	115 (96.08)	92.12 [63.32-175.2]	87.07; 142.9	54.78 (54.75)	63.32 [0-70.52]	32.67; 76.9	<0.01
Spirometry	71.24 (59.32)	63.32 [0-126.6]	54.01; 88.46	43.84 (43.02)	63.32 [0-63.32]	26.46; 61.21	0.06
skin test for allergy	7.8 (14.23)	0 [0-21.6]	3.667; 11.93	7.754 (13.03)	0 [0-28.8]	2.492; 13.02	0.90
blood test for allergy-specific IgE	25.95 (38.89)	0 [0-83.03]	14.65; 37.24	3.193 (16.28)	0 [0-0]	-3.384; 9.771	<0.01
chest X-rays	3.99 (12.15)	0 [0-0]	0.4631; 7.517	0 (0)	0 [0-0]	0; 0	0.06
ENT endoscopy	2.4 (8.044)	0 [0-0]	0.06422; 4.736	0 (0)	0 [0-0]	0; 0	0.14
pHmetry	3.6 (17.45)	0 [0-0]	-1.466; 8.666	0 (0)	0 [0-0]	0; 0	0.30
Day care unit admissions	102.5 (420.3)	0 [0-0]	-19.52; 224.6	0 (0)	0 [0-0]	0; 0	0.20
Emergency department visits	532.2 (1376)	0 [0-0]	132.7; 931.6	50.38 (256.9)	0 [0-0]	-53.38; 154.2	0.03
Hospitalizations	70.64 (277)	0 [0-0]	-9.784; 151.1	20.06 (102.3)	0 [0-0]	-21.25; 61.36	0.46
in emergency unit	21.73 (105.3)	0 [0-0]	-8.850; 52.30	20.06 (102.3)	0 [0-0]	-21.25; 61.36	0.97
in pulmonology unit	48.92 (260.4)	0 [0-0]	-26.69; 124.5	0 (0)	0 [0-0]	0; 0	0.30
Rehabilitation	344.7 (2188)	0 [0-0]	-290.6; 980	0 (0)	0 [0-0]	0; 0	0.30
Total	3821 (4350)	2126 [397.4-6182]	2557; 5084	297.7 (328.2)	211 [114.5-375.8]	165.1; 430.3	<0.01
Indirect costs							
Asthma-related School loss (days)	11.96 (21.34)	4.5 [2-11.5]	5.763; 18.15	1.75 (1.976)	1.5 [0-2]	0.9518; 2.548	<0.01
Asthma-related work loss of the father (€)	84.79 (191.9)	0 [0-148]	29.08; 140.5	25.62 (55.15)	0 [0-18.5]	3.341; 47.89	0.34
Asthma-related work loss of the father (days)	1.146 (2.593)	0 [0-2]	0.3929; 1.899	0.3462 (0.7452)	0 [0-0.25]	0.04514; 0.6472	0.34
Asthma-related work loss of the mother (€)	77.08 (133.0)	0 [0-148]	38.45; 115.7	39.85 (56.28)	0 [0-74]	17.11; 62.58	0.69
Asthma-related work loss of the mother (days)	1.042 (1.798)	0 [0-2]	0.5196; 1.564	0.5385 (0.7606)	0 [0-1]	0.2313; 0.8457	0.69
Total	161.9 (279.3)	0 [0-222]	80.79; 243.0	65.46 (92.01)	0 [0-92.5]	28.30; 102.6	0.38
Global Costs = Direct + Indirect Costs	3982 (4422)	2348 [498.8-6222]	2698; 5266	363.2 (352.6)	222.8 [150.3-460.3]	220.7; 505.6	<0.01

SA : severe asthma , NSA : son-severe asthma , IQR : interquartile range, ^aInhalation chamber, peak flow meter and nebulizer.

*Mann Whitney U.

Table 3. Estimated costs (€) for children with SA according to omalizumab treatment status during the six-month study period.

	SA with Omalizumab (n = 22)			SA without Omalizumab (n = 26)			p*
	Mean (SD)	Median [IQR]	95% CI	Mean (SD)	Median [IQR]	95% CI	
Direct costs							
Medications	5104 (3796)	4153 [1783 – 6806]	3421; 6787	281.7 (221.7)	251.2 [163.6-326.5]	192.2; 371.3	<0.01
Drugs	334.2 (149.3)	270.3 [252.9-423.5]	268; 400.5	277.4 (220.3)	251.2 [156-323.3]	188.5; 366.4	0.09
Anti-Ig E treatment	4745 (3742)	3878 [1408-6335]	3086; 6404	0 (0)	0 [0-0]	0; 0	<0.01
Immunotherapy	2042 (95.76)	0 [0-0]	-22.04; 62.87	0 (0)	0 [0-0]	0; 0	0.29
Influenza vaccination	459 (5.15)	0 [0-10.11]	2.31; 6.88	4.27 (5.09)	0 [0-10.11]	2.22; 6.33	0.83
Medical devices ^a	5726 (89.74)	8.84 [0-79.79]	17.47; 97.05	39.86 (82.9)	0 [0 – 11.05]	6.37; 73.34	0.11
Urgent (unscheduled) physician visit in ambulatory	48.86 (90.46)	25 [0-75]	8.75; 88.97	25.96 (39.67)	0 [0-56.25]	9.93; 41.99	0.31
Scheduled physician visits	81.95 (53.36)	80 [55.25-112]	58.3; 105.6	77.12 (59.27)	53.5 [28-115.5]	53.18; 101.1	0.5
Hospital outpatient visits	58.45 (42.01)	56 [28-91]	39.83; 77.08	52.54 (42.14)	28 [28-72.75]	35.52; 69.56	0.5
To pulmonologist/allergist	50.82 (37)	56 [28-84]	34.41; 67.22	50.38 (41.89)	28 [28-69]	33.46; 67.31	0.74
To another specialist	7.63 (17.67)	0 [0-0]	-0.19; 15.47	2.15 (10.98)	0 [0-0]	-2.28; 6.59	0.12
Ambulatory visits	23.5 (38.69)	0 [0-48]	6.34; 40.66	24.58 (42.85)	0 [0-48]	7.268; 41.89	0.96
To general practitioner	14.77 (37.53)	0 [0-0]	-1.866; 31.41	1.92 (6.79)	0 [0-0]	-0.82; 4.66	0.24
To pediatrician	0 (0)	0 [0-0]	0; 0	8.84 (25.26)	0 [0-0]	-1.35; 19.05	0.06
To another specialist	8.72 (18.95)	0 [0-0]	0.3257; 17.13	13.81 (28.79)	0 [0-12]	2.178; 25.44	0.64
Outpatient Clinical and Laboratory tests	115.3 (98.56)	87.58 [47.49-190.0]	71.6; 159	114.7 (89.58)	92.12 [63.32-160.4]	75.96; 153.4	0.99
spirometry	80.59 (65.34)	63.32 [0-126.6]	51.62; 109.6	63.32 (53.73)	63.32 [0-63.32]	41.62; 85.02	0.35
skin test for allergy	3.92 (10.12)	0 [0-0]	-0.5579; 8.412	11.08 (16.45)	0 [0-28.80]	4.434; 17.72	0.09
blood test for allergy-specific IgE	22.64 (37.85)	0 [0-83.03]	5.863; 49.43	28.74 (40.28)	0 [0-83.03]	12.47; 45.01	0.59
chest X-rays	2.9 (13.61)	0 [0-0]	-3.133; 8.936	4.91 (10.95)	0 [0-0]	0.4893; 4.332	0.15
ENT endoscopy	1.309 (6.14)	0 [0-0]	-1.413; 4.032	3.323 (9.383)	0 [0-0]	-0.467; 7.113	0.39
pHmetry	3.92 (18.42)	0 [0-0]	-4.24; 12.09	3.32 (16.94)	0 [0-0]	-3.521; 10.17	0.92
Day care unit admissions	94.4 (442.8)	0 [0-0]	-101.9; 290.7	109.4 (409)	0 [0-0]	-55.82; 274.6	0.71
Emergency department visits	952.7 (1839)	0 [0-1474]	137.6; 1768	176.3 (656.5)	0 [0-0]	-88.82; 441.5	0.04
Hospitalizations	77.04 (199.8)	0 [0-0]	-11.55; 165.6	65.23 (332.6)	0 [0-0]	-69.11; 199.6	0.26
in emergency unit	47.4 (153.4)	0 [0-0]	20.62; 115.4	0 (0)	0 [0-0]	0; 0	0.12
in pulmonology unit	29.64 (139)	0 [0-0]	-32; 91.27	65.23 (332.6)	0 [0-0]	-69.11; 199.6	0.95
Rehabilitation (Cure therapy)	0 (0)	0 [0-0]	0; 0	636.4 (2967)	0 [0-0]	-562.2; 1835	0.16
Total	6531 (4101)	6087 [3296-9382]	4713; 8350	1527 (3084)	434.6 [259-1404]	281.0; 2772	<0.01
Indirect costs							
Asthma-related School loss (days)	20.0 (28.81)	6.5 [2-30.25]	7.2; 32.7	5.53 (7.55)	4 [1.75-5.5]	2.4; 8.5	0.09
Asthma-related work loss of the father (€)	94.18 (255.5)	0 [0-37]	-19.11; 207.5	76.85 (119.3)	0 [0-166.5]	28.67; 125.0	0.40
Asthma-related work loss of the father (days)	1.27 (3.45)	0 [0-0.5]	-0.2582; 2.804	1.038 (1.61)	0 [0-2.25]	0.3874; 1.69	0.40
Asthma-related work loss of the mother (€)	90.82 (153.1)	0 [0-166.5]	22.95; 158.7	65.46 (115.3)	0 [0-148]	18.91; 112.0	0.97
Asthma-related work loss of the mother (days)	1.22 (2.06)	0 [0-2.25]	0.3101; 2.144	0.88 (1.55)	0 [0-2]	0.2555; 1.514	0.97
Total	185.0 (365.9)	0 [0-240.5]	22.76; 347.2	142.3 (182.4)	111.0 [0-240.5]	68.65; 216.0	0.50
Global Costs = Direct + Indirect costs	6716 (4220)	6163 [3296-10039]	4845; 8588	1669 (3108)	650.8 [324.9-1626]	413.6; 2924	<0.01

SA : severe asthma , IQR : interquartile range, ^a inhalation chamber, peak flow meter and nebulizer, ENT : ear nose throat.

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Table 4. Medication costs (€) according to asthma severity during the six-month study period.

	Mean (SD)	SA (n = 48) Median [IQR]	95% CI	Mean (SD)	NSA (n = 26) Median [IQR]	95% CI	p*
Medications							
Influenza vaccination	4.423 (5.068)	0 [0-10.11]	2.951; 5.895	3.5 (4.905)	0 [0-10.11]	1.518; 5.481	0.45
Asthma Rescue treatment							
SABA (MDI or DPI)	19.93 (18.29)	13.46 [8.073-24.84]	14.62; 25.24	6.468 (3.997)	5.382 [2.691-10.76]	4.853; 8.082	<0.01
SABA (nebulizer solution)	16.68 (52.71)	0 [0-11.56]	1.374; 31.98	0.4445 (2.267)	0 [0-0]	-0.471; 1.360	<0.01
Ipratropium bromide in nebulizer solution	4.932 (16.97)	0 [0-0]	0.005628; 9.858	0 (0)	0 [0-0]	0; 0	0.04
Oral corticosteroids	4.99 (4.719)	2.405 [2.405-7.215]	3.604; 3.604	1.728 (2.309)	0.8125 [0-2.405]	0.7949; 2.660	<0.01
Asthma Maintenance treatment							
Inhaled corticosteroid (+/- LABA) treatment (MDI, DPI)	124.5 (66.81)	141.4 [80.82-149.2]	105.1; 143.9	64.16 (57.08)	54.43 [12.43-116.3]	41.1; 87.21	<0.01
Inhaled corticosteroid (MDI or DPI)	24.92 (67.42)	0 [0-0]	5.337; 44.49	4.625 (11.11)	0 [0-1.243]	0.1368; 9.114	0.73
Inhaled corticosteroid + LABA (MDI or DPI)	99.61 (70.53)	134.5 [28.02-149.2]	79.13; 120.1	59.53 (60.89)	54.43 [0-116.3]	34.94; 84.13	<0.01
Inhaled corticosteroid (nebulizer solution)	35.97 (91.27)	0 [0-0]	9.467; 62.47	0 (0)	0 [0-0]	0; 0	0.01
Isolated LABA treatment (MDI or DPI)	10.65 (26.85)	0 [0-0]	2.853; 18.44	0 (0)	0 [0-0]	0; 0	0.04
Leukotriene modifiers	46.1 (45.16)	44.56 [0-89.12]	32.99; 59.22	7.426 (26.32)	0 [0-0]	-3.204; 18.06	0.01
Long- term antibiotic treatment	2.596 (10.91)	0 [0-0]	-0.5714; 5.764	0 (0)	0 [0-0]	0; 0	0.20
Anti-Ig E treatment	2175 (3459)	0 [0-3353]	1170; 3179	0 (0)	0 [0-0]	0; 0	<0.01
Comorbidity treatment							
Proton-pump inhibitors	8.542 (18.03)	0 [0-2.340]	3.306; 13.78	1.368 (6.973)	0 [0-0]	-1.449; 4.184	0.03
Oral antihistamines	4.662 (4.110)	4.941 [0-8.546]	3.469; 5.856	2.692 (3.49)	0 [0- 6.069]	1.282; 4.102	0.03
Anti-allergic eye drops	0.8099 (2.078)	0 [0-0.84]	0.1702; 1.45	0.04759 (0.2232)	0 [0-0]	-0.05138; 0.1466	0.03
Steroid nasal sprays	4.378 (4.874)	2.117 [0-10.80]	2.963; 5.793	1.554 (2.994)	0 [0-1.8]	0.3453; 2.764	0.02
Adrenaline pens	18.9 (68.83)	0 [0-0]	-1.085; 38.89	5.323 (27.14)	0 [0-0]	-5.64; 16.29	0.34
Allergen Immunotherapy	9.357 (64.83)	0 [0-0]	-9.467; 28.18	32.23 (105.3)	0 [0-0]	-10.32; 74.78	0.04
TOTAL	2492 (3516)	505.4 [216.7-3634]	1471; 3513	126.9 (154.4)	93.39 [25.26-163.1]	64.57; 189.3	<0.01

SA: severe asthma, NSA: non-severe asthma, IQR: interquartile range, CI: confidence interval, 95% CI = lower 95% CI of the mean; upper 95% CI of the mean, SD: standard deviation, SABA: short-acting beta-2 agonist, LABA: long-acting beta-2 agonist, DPI: dry powder inhaler, MDI: metered dose inhaler.

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for those who were not. The costs of ED visits for the NHI were higher for children with SA than those with NSA (€532.2 (1,376) vs. €50.38 (256.9), $p = 0.03$).

Hospitalizations/admissions

Hospitalization costs did not differ between children with SA, regardless of omalizumab treatment, and between children with SA and those with NSA (see [supplemental information](#) for more details).

Rehabilitation

Rehabilitation accounted for 9% of direct costs (€344.7 (2188) per child) for children with SA. Two children with SA (not under omalizumab) were admitted to a rehabilitation center. One had continuous inpatient care throughout the year for which the cost to the NHI was €15 121.19. The other was admitted for a two-week period, for which the cost to the NHI was €1,424.05. Rehabilitation accounted for 8.6% of global costs for all children with SA considered together but increased to 38% of global costs for children with SA not under omalizumab treatment.

Outpatient clinical and laboratory tests

Total cost related to outpatient clinical and laboratory tests was higher in children with SA vs. NSA (€115.0 (96.08) vs. €54.78 (54.75), $p < 0.01$) ([Table 2](#)) (see [supplemental information](#) for full details).

Indirect costs

The costs for asthma-related work loss did not differ between parents of children with SA and those with NSA ([Table 2](#)). Indirect costs did not differ between children with SA with or without omalizumab ([Table 3](#)). Among the parents of children with SA, mothers only adapted their lifestyle because of their child's disease. Four did not have a job, four declared that they could not work or had to stop working because of their child's disease, and four declared to work at home because of her child's SA. Asthma-related school absenteeism was higher for children with SA than children with NSA (11.96 days (21.34) vs. 1.75 days (1.976), $p < 0.01$).

Global costs

The global cost per child with SA was €3,982 (4422) over the six-month study period ([Table 2](#)). The global cost was four times higher for children requiring

omalizumab than those who did not (€6,716 (4,220) vs. €1,669 (3,108), $p < 0.01$) ([Table 3](#)).

The global cost per child with asthma was approximately 10 times higher for children with SA than those with NSA (€3,982 (4,422) vs. €363.2 (352.6), $p < 0.01$) and approximately 20 times higher for children with SA under omalizumab treatment than those with NSA (€6,716 (4,220) vs. €363.2 (352.6), $p < 0.01$) ([Figure 1](#)).

Discussion

The aim of this study was to assess the healthcare costs of children with SA for the French NHI, based on individual evaluation of asthma-related costs over a six-month period. The originality of our approach was that a) we first selected a sample of children with physician-confirmed asthma, b) a bottom-up approach was adopted, starting from well-defined patients with asthma, to assess the economic burden of asthma at the individual level, c) a large set of variables reflecting the global costs of asthma and associated comorbidities were analyzed, and d) the costs of biologics, immunizations, and rehabilitation were assessed. The global cost of SA in children for the French NHI was €3,982 per child over a six-month period, including €3,821 for direct costs and €161.9 for indirect costs. This figure only partially reflects the economic burden of SA because the global cost was four times higher for children requiring omalizumab than for those who did not. Most of the direct costs for patients with SA were for medication and, to a lesser extent, ED visits and rehabilitation. For children with SA under omalizumab treatment, this therapy accounted for 93% of medication expenditures, 73% of direct costs, and 71% of the global cost. The global cost of asthma was approximately ten times higher for children with SA than those with NSA. The costs associated with asthma-related work loss did not differ between parents of children with SA and NSA.

Our results support previous studies showing that the annual cost of asthma increase with asthma severity (5,7,8,10,12,14,15,30–32). In Germany, the total annual cost per child was €2,202 for children with moderate asthma and €7,928 for those with SA (7). The annual costs of asthma for Spanish children was approximately fifteen times higher for those with SA, ranging from €403 for children with mild asthma to €5,380 for those with SA (8). Our results highlight that the cost differs widely among children with SA. The global cost of SA is mainly driven by children with the most severe phenotype, requiring the

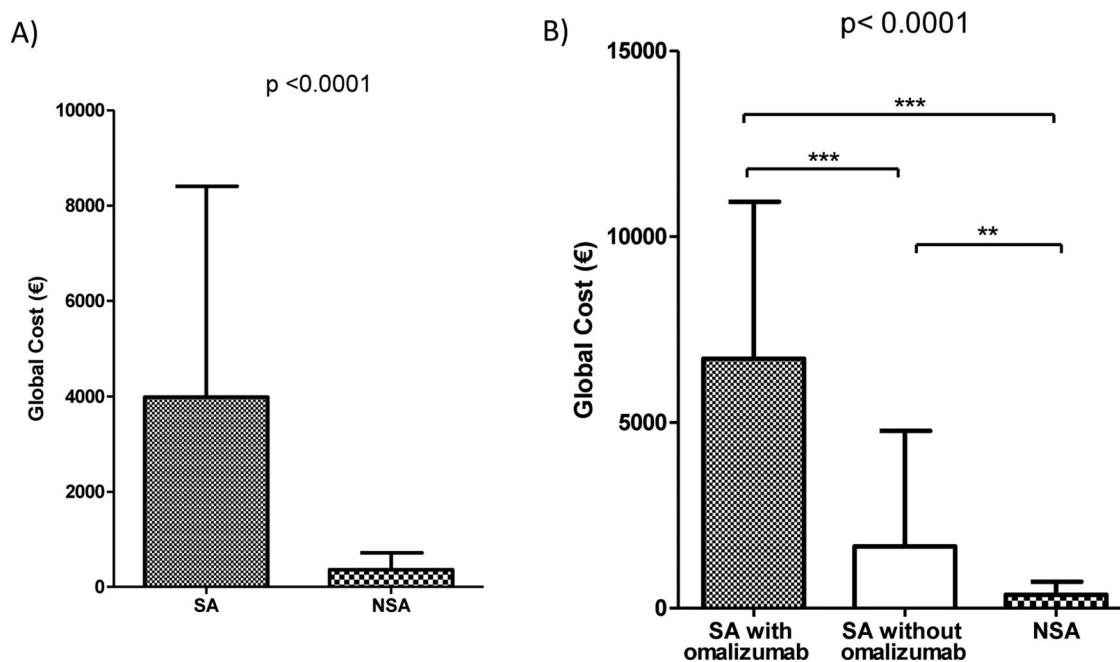


Figure 1. Global costs (mean $\pm$ SD; €) of asthma according to (A) asthma severity and (B) asthma severity and omalizumab treatment status during the six-month study period.

prescription of biologics. However, regardless of omalizumab use, the economic burden of children with SA remained higher than that of children NSA. This was mostly due to ED visits, rehabilitation costs, and outpatient clinical and laboratory tests, although the costs for anti-asthma medications, scheduled physician visits, unscheduled ambulatory physician visits, and medical devices were also higher than those for children with NSA.

Although differences in methodology, selection of populations, and funding systems makes it difficult to compare studies, direct costs for children with SA were substantially higher than those previously published, in which they were estimated to range between €1,440.75 and €2,460 per patient per year (5,33,34). The use of biologics, which was uncommon in previous studies, may explain a large part of this difference. In our study, omalizumab was the main driver of costs for children with SA. Outside of the use of omalizumab, the costs attributed to all other medications and hospitalization were similar for children with SA.

The costs attributed to ED visits were the second largest component of healthcare costs in children with SA. ED visits accounted for 14.1% of the global cost for children with SA under omalizumab treatment and decreased to 10.5% for those who were not. This result supports that children who were prescribed omalizumab had a more severe phenotype. On the other hand, some children started omalizumab a few weeks before inclusion and others during the study

period. Given the efficacy of omalizumab in the reduction of severe exacerbations (35), this suggests that the effect of omalizumab was not yet completely achieved at least in some children. Two children with SA were treated in a rehabilitation center. Rehabilitation represented 38% (€636.4) of the global cost in this group, and globally, 9% of direct costs and 8.6% of the global cost. In a previous study, rehabilitation accounted for 49.8% of asthma-related total direct costs in children (5). This may reflect differences in practice, health systems between countries, the availability of rehabilitation centers, or the use of medication, including biologics, for the most symptomatic children.

The costs of asthma-related work loss did not differ between parents of children with SA and those with NSA. The study period was possibly too short to highlight such a difference. However, this finding may result from the fact that some mothers of children with SA adapted their lifestyle as a consequence of the severity of the disease. Several mothers declared that they had to stop working or to work at home to take better care of their child. This also suggests SA may result in parental loss of incomes.

This study is the first to assess the healthcare costs of SA in children for the French NHI. One of its strengths is that we first identified children with physician-confirmed SA and then we estimated health expenditures related to asthma in this selected population. This approach reduces the risk of misestimation of the diagnosis of SA by algorithms based on the use

of asthma-related healthcare resources (10,13). In addition, we included certain costs rarely considered in previous studies, such as the cost of flu vaccinations, rehabilitation stays, outpatient clinical and laboratory tests, ENT endoscopy, and esophageal pH monitoring. Our study also had several limitations. First, our sample was small. However, the population was well defined, the diagnosis of SA was confirmed by physicians, and a deep analysis of a large set of variables was performed, including the costs of comorbidities frequently associated with asthma, reflecting the global economic burden of asthma disease. In the absence of randomization, there is a risk of selection bias. Children were thus recruited at random on the day of their consultation to limit this bias. Although children were recruited in a single center, in France, children with SA are generally followed in tertiary-care centers, such as our department. Finally, our sample included children with SA receiving, or not, omalizumab, providing a real-life picture of children with SA. Our estimation was based on parental declarations. A resulting memory bias is therefore possible, with parents under- or over-reporting certain expenditures, or indirect costs such as school and work loss days. We limited this risk by including children who were regularly followed-up in the department, using a physician-guided parental questionnaire, covering only a short period of time for the assessments, and confirming the parental declarations by analyzing the medical records. The best design would have been to obtain the data of children selected by a physician from the NHI. However, this approach is rarely, if ever, authorized in France. Moreover, our study period included winter and spring, i.e. the seasons during which asthma exacerbations are frequent. This may have led to an overestimation of healthcare costs, such as those related to ED visits and steroid or antihistamine use. Certain costs, such as those related to transportation, may have been underestimated. Although the use of medical transport or emergency transportation to emergency rooms were not analyzed, children with SA rarely use such means to reach the ED.

In summary, our findings show that the economic burden of children with SA for the French NHI is substantial and mainly driven by children with the most severe phenotype. The social and economic consequences of SA on parental life deserve the full attention of medical teams.

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Declaration of interest

The authors have indicated they have no potential conflicts of interest to disclose.

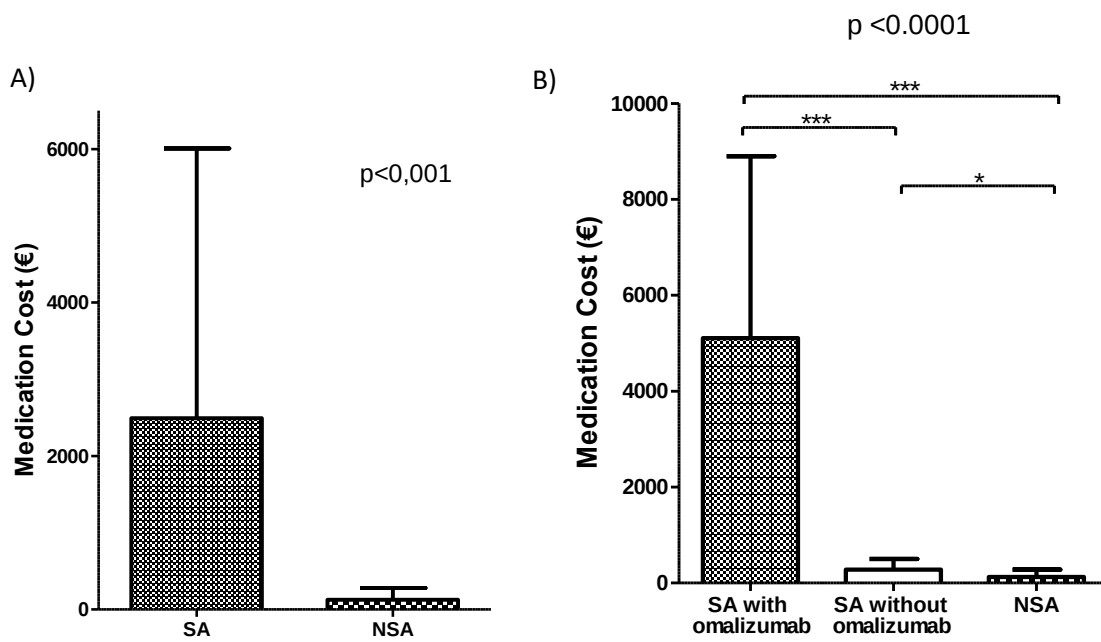
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Supplemental Figure 1. Medication costs (mean $\pm$ SD, €) of asthma according to (A) asthma severity and (B) asthma severity and omalizumab treatment status. S: severe asthma, NSA: non-severe asthma. * $p < 0.01$, ** $p < 0.001$, * $p < 0.0001$.**

Supplemental Table 1. General characteristics of children with SA according to omalizumab treatment status.

Characteristics	SA	SA with omalizumab	SA without omalizumab	P
N	48	22	26	
Gender				
Male/female	30/18	15	15	0.46
Age (years)	13.4 [10.73 - 16.18]	14.2 [11.15 - 16.6]	12.8 [10.08 - 15.9]	0.23
6-12	17 (35.4%)	6 (27.2%)	11 (42.3%)	
≥ 12	31 (64.6%)	16 (72.7%)	15 (57.6%)	0.28
BMI (kg/m ²)	19.37 [17.14 - 21.91]	19.48 [17.59 - 21.78]	18.86 [17.02 - 22.08]	0.82
Atopy, n (%)	39 (81.2%)	22 (100%)	17 (65.3%)	0.01
Comorbid diseases				
Atopic dermatitis	15 (31.2%)	9 (40.9%)	6 (23%)	0.19
Food allergy	8 (16.6%)	5 (22.7%)	3 (11.5%)	0.31
Allergic rhinitis+/- conjunctivitis	37 (77%)	19 (86.3%)	18 (69.2%)	0.16
Nasal polyps	1 (2.1%)	0	1 (3.8%)	0.37
Sinusitis	3 (6.3%)	1 (4.5%)	1 (3.8%)	0.67
Gastroesophageal reflux disease	14 (29.1%)	8 (36.3%)	6 (23%)	0.32
Obstructive sleep apnea syndrome	1 (2.1%)	0	1 (3.8%)	0.37
Influenza vaccination, n (%)	21 (43.7%)	10 (45.4%)	11 (42.3%)	0.83
Utilization of treatments				
ICS treatment	48 (100%)	22 (100%)	26 (100%)	<0.01
Dose of ICS (µg/d flu eq.)	500 [500-500]	500 [500-500]	500 [362.5-500]	0.059
LABA, n (%)	42 (87.5%)	18 (81.8%)	24 (92.3%)	0.28
Nebulization for maintenance treatment, n (%)	7 (14.6%)	3 (13.6%)	4 (15.3%)	0.87
Leukotriene antagonist, n (%)	26 (54.1%)	15 (68.1%)	11 (42.3%)	0.078
Long term antibiotic treatment, n (%)	3 (6.3%)	1 (4.5%)	2 (7.6%)	0.67

Anti-Ig E, n (%)	22 (45.8%)	22 (100%)	0	<0.01
Allergen Immunotherapy, n (%)	1 (2.1%)	1 (4.5%)	0	0.29
Rehabilitation, n (%)	2 (4.2%)	0	2 (7.6%)	0.19
Patients with outpatient clinical and laboratory tests, n (%)				
Spirometry	35 (72.9%)	16 (72.7%)	19 (73%)	0.98
At hospital	35 (72.9%)	16 (72.7%)	19 (73%)	0.98
In ambulatory	1 (2.1%)	0	1 (3.8%)	0.37
skin test for allergy	12 (25%)	3 (13.6%)	9 (34.6%)	0.1
blood test for allergy-specific IgE	15 (31.2%)	6 (27.2%)	9 (34.6%)	0.59
chest X-ray	6 (12.5%)	1 (4.5%)	5 (19.2%)	0.13
ENT endoscopy	4 (8.4%)	1 (4.5%)	3 (11.5%)	0.39
PHmetry	2 (4.2%)	1 (4.5%)	1 (3.8%)	0.92
Emergency department visit, n (%)	11 (22.9%)	8 (36.3%)	3 (11.5%)	0.05
Emergency department visit per patient	0.23	0.36	0.12	
Day Care Unit admission, n (%)	3 (6.3%)	1 (4.5%)	2 (7.6%)	0.67
Hospitalization, n (%)	4 (8.4%)	3 (13.6%)	1 (3.8%)	0.23
in emergency department	2 (4.2%)	2 (9%)	0	0.12
in pulmonology department	2 (4.2%)	1 (4.5%)	1 (3.8%)	0.92
Urgent (unscheduled) physician ambulatory visit, n (%)	21 (43.7%)	12 (54.5%)	9 (34.6%)	0.17
Scheduled physician visit, n (%)				
Hospital outpatient visit				
To pulmonologist/allergist	43 (89.6%)	18 (81.8%)	25 (96.1%)	0.11
To ENT specialist	4 (8.4%)	3 (13.6%)	1 (4.1%)	0.26
To dermatologist	2 (4.2%)	2 (9%)	0	0.14
To ophthalmologist	1 (2.1%)	0	1 (4.1%)	0.36
Ambulatory visit				

To general practitioner	6 (12.5%)	4 (18.1%)	2 (7.6%)	0.28
To pediatrician	4 (8.4%)	0	4 (15.3%)	0.06
To pulmonologist	4 (8.4%)	2 (9%)	2 (7.6%)	0.87
To allergist	1 (2.1%)	1 (4.5%)	0	0.29
To ENT specialist	5 (10.4%)	0	5 (19.2%)	0.03
To ophthalmologist	1 (2.1%)	1 (4.5%)	0	0.29

Data are expressed as the median [25% -75%] or n (%)

SA: severe asthma , NSA: non-severe asthma, BMI : Body Mass Index, ICS : inhaled corticosteroids, $\mu\text{g}/\text{d}$ flu eq : $\mu\text{g}/\text{day}$ in fluticasone equivalent^a in fluticasone equivalent, LABA: long-acting beta-2 agonist, ENT : ear nose throat

Supplemental Table 2. Estimated costs (€) of asthma according to asthma severity and omalizumab treatment status during the six-month study period.

	SA with Omalizumab (n=22)			SA without Omalizumab (n=26)			NSA (n=26)			p*
	Mean (SD)	Median [IQR]	95% CI	Mean (SD)	Median [IQR]	95% CI	Mean (SD)	Median [IQR]	95% CI	
Direct costs										
Medications	5104 (3796)	4153 [1783 -6806]	3421; 6787	281.7 (221.7)	251.2 [163.6-326.5]	192.2; 371.3	126.9 (154.4)	93.39 [25.26-163.1]	64.57; 189.3	<0.01
Drugs	334.2 (149.3)	270.3 [252.9-423.5]	268; 400.5	277.4 (220.3)	251.2 [156-323.3]	188.5; 366.4	91.20 (81.14)	80.16 [19.04-136.4]	58.43; 124	< 0.01
Anti-Ig E treatment	4745 (3742)	3878 [1408-6335]	3086; 6404	0 (0)	0 [0-0]	0; 0	0 (0)	0 [0-0]	0; 0	< 0.01
Immunotherapy	20.42 (95.76)	0 [0-0]	- 22.04; 62.87	0 (0)	0 [0-0]	0; 0	32.23 (105.3)	0 [0-0]	- 10.32; 74.78	0.09
Influenza vaccination	4.59 (5.15)	0 [0-10.11]	2.31; 6.88	4.27 (5.09)	0 [0-10.11]	2.22; 6.33	3.5 (4.905)	0 [0-10.11]	1.518; 5.481	0.73
Medical devices ^a	57.26 (89.74)	8.84 [0-79.79]	17.47; 97.05	39.86 (82.9)	0 [0 -11.05]	6.37; 73.34	2.04 (3.798)	0 [0-2.21]	0.5058; 3.574	0.01
Urgent (unscheduled) physician visit in ambulatory	48.86 (90.46)	25 [0-75]	8.75; 88.97	25.96 (39.67)	0 [0-56.25]	9.93; 41.99	1.923 (6.794)	0 [0-0]	- 0.8209; 4.667	<0.01
Scheduled physician visits	81.95 (53.36)	80 [55.25-112]	58.3; 105.6	77.12 (59.27)	53.5 [28-115.5]	53.18; 101.1	41.58 (33.71)	28 [27.25-59.75]	27.96; 55.19	<0.01
Hospital outpatient visits	58.45 (42.01)	56 [28-91]	39.83; 77.08	52.54 (42.14)	28 [28-72.75]	35.52; 69.56	25.77 (27.99)	28 [0-28]	14.46; 37.07	<0.01
To pulmonologist/allergist	50.82 (37)	56 [28-84]	34.41; 67.22	50.38 (41.89)	28 [28-69]	33.46; 67.31	24.69 (24.32)	28 [0-69]	14.87; 34.51	<0.01
To another specialist	7.63 (17.67)	0 [0-0]	- 0.19; 15.47	2.15 (10.98)	0 [0-0]	- 2.28; 6.59	1.077 (5.491)	0 [0-0]	- 1.141; 3.295	0.12

Ambulatory visits	23.5 (38.69)	0 [0-48]	6.34; 40.66	24.58 (42.85)	0 [0-48]	7.268; 41.89	15.81 (23.51)	0 [0-48]	6.313; 25.3	0.94
To general practitioner	14.77 (37.53)	0 [0-0]	- 1.866; 31.41	1.92 (6.79)	0 [0-0]	- 0.82; 4.66	3.846 (11.6)	0 [0-0]	- 0.8402; 8.532	0.46
To pediatrician	0 (0)	0 [0-0]	0; 0	8.84 (25.26)	0 [0-0]	- 1.35; 19.05	0 (0)	0 [0-0]	0; 0	0.02
To another specialist	8.72 (18.95)	0 [0-0]	0.3257; 17.13	13.81 (28.79)	0 [0-12]	2.178; 25.44	11.96 (22.66)	0 [0-12]	2.808; 21.12	0.87
Outpatient Clinical and Laboratory tests	115.3 (98.56)	87.58 [47.49- 190.0]	71.6; 159	114.7 (895.89)	92.12 [63.32- 160.4]	75.96; 153.4	54.78 (54.75)	63.32 [0- 70.52]	32.67; 76.9	0.02
spirometry	80.59 (65.34)	63.32 [0- 126.6]	51.62; 109.6	63.32 (53.73)	63.32 [0-63.32]	41.62; 85.02	43.84 (43.02)	63.32 [0- 63.32]	26.46; 61.21	0.11
skin test for allergy	3.92 (10.12)	0 [0-0]	- 0.5579; 8.412	11.08 (16.45)	0 [0-28.80]	4.434; 17.72	7.754 (13.03)	0 [0-28.8]	2.492; 13.02	0.24
blood test for allergy-specific IgE	22.64 (37.85)	0 [0-83.03]	5.863; 49.43	28.74 (40.28)	0 [0-83.03]	12.47; 45.01	3.193 (16.28)	0 [0-0]	- 3.384; 9.771	0.02
chest X-rays	2.9 (13.61)	0 [0-0]	- 3.133; 8.936	4.91 (10.95)	0 [0-0]	0.4893; 4.332	0 (0)	0 [0-0]	0; 0	0.04
ENT endoscopy	1.309 (6.14)	0 [0-0]	- 1.413; 4.032	3.323 (9.383)	0 [0-0]	- 0.467; 7.113	0 (0)	0 [0-0]	0; 0	0.18
pHmetry	3.92 (18.42)	0 [0-0]	- 4.24; 12.09	3.32 (16.94)	0 [0-0]	- 3.521; 10.17	0 (0)	0 [0-0]	0; 0	0.57
Day care unit admissions	94.4 (442.8)	0 [0-0]	- 101.9; 290.7	109.4 (409)	0 [0-0]	- 55.82; 274.6	0 (0)	0 [0-0]	0; 0	0.38
Emergency department visits	952.7 (1839)	0 [0-1474]	137.6; 1768	176.3 (656.5)	0 [0-0]	- 88.82; 441.5	50.38 (256.9)	0 [0-0]	- 53.38; 154.2	<0.01
Hospitalizations	77.04 (199.8)	0 [0-0]	- 11.55; 165.6	65.23 (332.6)	0 [0-0]	- 69.11; 199.6	20.06 (102.3)	0 [0-0]	- 21.25; 61.36	0.33
in emergency department	47.4 (153.4)	0 [0-0]	20.62; 115.4	0 (0)	0 [0-0]	0; 0	20.06 (102.3)	0 [0-0]	- 21.25;	0.29

									61.36	
in pulmonology department	29.64 (139)	0 [0-0]	- 32; 91.27	65.23 (332.6)	0 [0-0]	- 69.11;19 9.6	0 (0)	0 [0-0]	0; 0	0.57
Rehabilitation	0 (0)	0 [0-0]	0; 0	636.4 (2967)	0 [0-0]	- 562.2; 1835	0 (0)	0 [0-0]	0; 0	0.13
Total	6531 (4101)	6087 [3296-9382]	4713; 8350	1527 (3084)	434.6 [259-1404]	281.0; 2772	297.7 (328.2)	211 [114.5-375.8]	165.1; 430.3	< 0.01
Indirect costs										
<i>Asthma-related School loss (days)</i>	20.0 (28.81)	6.5 [2-30.25]	7.2; 32.7	5.53 (7.55)	4 [1.75-5.5]	2.4; 8.5	1.75 (1.976)	1.5 [0-2]	0.9518; 2.548	<0.01
Asthma-related work loss of the father (€)	94.18 (255.5)	0 [0-37]	- 19.11; 207.5	76.85 (119.3)	0 [0-166.5]	28.67; 125.0	25.62 (55.15)	0 [0-18.5]	3.341; 47.89	0.41
<i>Asthma-related work loss of the father (days)</i>	1.27 (3.45)	0 [0-0.5]	- 0.2582; 2.804	1.038 (1.61)	0 [0-2.25]	0.3874; 1.69	0.3462 (0.7452)	0 [0-0.25]	0.04514 ; 0.6472	0.41
Asthma-related work loss of the mother (€)	90.82 (153.1)	0 [0-166.5]	22.95; 158.7	65.46 (115.3)	0 [0-148]	18.91; 112.0	39.85 (56.28)	0 [0-74]	17.11; 62.58	0.92
<i>Asthma-related work loss of the mother (days)</i>	1.22 (2.06)	0 [0-2.25]	0.3101; 2.144	0.88 (1.55)	0 [0-2]	0.2555 ; 1.514	0.5385 (0.76)	0 [0-1]	0.2313; 0.8457	0.92
Total	185.0 (365.9)	0 [0-240.5]	22.76; 347.2	142.3 (182.4)	111.0 [0-240.5]	68.65; 216.0	65.46 (92.01)	0 [0-92.5]	28.30; 102.6	0.43
Global Costs = Direct + Indirect costs	6716 (4220)	6163 [3296-10039]	4845; 8588	1669 (3108)	650.8 [324.9-1626]	413.6; 2924	363.2 (352.6)	222.8 [150.3-460.3]	220.7; 505.6	< 0.01

SA : severe asthma , IQR : interquartile range, CI : confidence interval, 95% CI : lower 95% CI of the mean; upper 95% CI of the mean, SD : standard deviation, ° inhalation chamber, peak flow meter and nebulizer, ENT : ear nose throat

* Kruskal Wallis

Supplemental Table 3. Medication Costs (€) of children with SA according to omalizumab treatment status during the six-month study period.

	SA with Omalizumab (n=22)			SA without Omalizumab (n=26)			p*
	Mean (SD)	Median [IQR]	95% CI	Mean (SD)	Median [IQR]	95% CI	
Medications							
Influenza vaccination	4.59 (5.15)	0 [0 - 10.11]	2.311; 6.88	4.27 (5.09)	0 [0 - 10.11]	2.22; 6.335	0.83
Asthma Rescue treatment							
SABA (MDI or DPI)	27.09 (19.25)	21.11 [10.76 - 38.35]	18.55; 35.62	13.87 (15.3)	9.93 [7.57 - 16.15]	7.688; 20.05	<0.01
SABA (nebulizer solution)	11.02 (21.54)	0 [0 - 14.45]	1.468; 20.57	21.47 (69.15)	0 [0 - 11.56]	- 6.46; 49.40	0.62
Ipratropium bromide in nebulizer solution	0.35 (1.68)	0 [0 - 0]	- 0.3872; 1.105	8.80 (22.47)	0 [0 - 1.97]	- 0.273; 17.88	0.06
Oral corticosteroids	4.69 (4.19)	4.81 [2.40 - 7.21]	2.784; 6.607	5.22 (5.17)	2.40 [2.40 - 7.21]	3.138; 7.316	0.95
Asthma Maintenance treatment							
Inhaled corticosteroid (+/- LABA) treatment (MDI, DPI)	138.8 (64.9)	148 [128.9 - 149.2]	110; 176.5	112.5 (67.2)	134.5 [57.42 - 149.2]	85.34; 139.6	0.13
Inhaled corticosteroid (MDI or DPI)	38.56 (89.22)	0 [0 - 0]	- 1.001, 78.11	13,37 (39.47)	0 [0 - 0]	- 2.569; 29.32	0.67
Inhaled corticosteroid + LABA (MDI or DPI)	100.2 (65.89)	134.5 [0 - 149.2]	70.94; 129.4	99.12 (75.46)	127.7 [39.23 - 149.2]	68.64; 129.6	0.77
Inhaled corticosteroid (nebulizer solution)	32.6 (79.02)	0 [0 - 0]	- 2.43; 67.64	38.82 (102)	0 [0 - 3.07]	- 2.36; 80.0	0.75
LABA treatment (MDI or DPI)	8.5 (22.89)	0 [0 - 0]	- 1.64; 18.65	12.47 (30.13)	0 [0 - 0]	0.29; 24.64	0.8
Leukotriene modifiers	56.71 (42.66)	89.12 [0 - 89.12]	37.79; 75.63	37.13 (46.07)	0 [0 - 89.12]	18.52; 55.74	0.22
Long term antibiotic treatment	2.76 (12.94)	0 [0 - 0]	- 2.978; 8.495	2.46 (9.12)	0 [0 - 0]	- 1.223; 6.141	0.71
Anti-Ig E treatment	4745 (3742)	3878 [1408 - 6335]	3086; 6404	0 (0)	0 [0 - 0]	0;0	<0.01
Comorbidity treatment							
Proton pump inhibitors	9.01 (17.57)	0 [0 - 16.75]	1.225; 16.80	8.14 (18.76)	0 [0 - 0.78]	0.5668; 15.72	0.73
Oral antihistamines	6.85 (4.07)	7.59 [4.55 - 8.56]	5.046; 8.658	2.81 (3.17)	1.75 [0- 5.24]	1.53; 4.089	<0.01
Anti-allergic eye drops	1.44 (2.9)	0 [0 - 1.53]	0.080; 2.795	0.26 (0.56)	0 [0 - 0]	0.0226; 0.5051	0.19

Steroid nasal sprays	5.73 (5.64)	6.09 [0 - 10.80]	3.232; 8.23	3.23 (3.87)	1.80 [0 - 5.40]	1.669; 4.798	0.21
Adrenaline pens	29.08 (96.02)	0 [0 - 0]	- 13.46; 71.65	10.29 (31.54)	0 [0 - 0]	- 2.449; 23.3	0.89
Allergen Immunotherapy	20.42 (95.76)	0 [0 - 0]	- 22.04; 62.87	0 (0)	0 [0 - 0]	0; 0	0.29
TOTAL	5104 (3796)	4153 [1783 -6806]	3421; 6787	281.7 (221.7)	251.2 [163.6 - 326.5]	192.2; 371.3	<0.01

SA: severe asthma , NSA: non-severe asthma, IQR: interquartile range, CI: confidence interval, 95% CI = lower 95% CI of the mean; upper 95% CI of the mean, SD: standard deviation, SABA: short-acting beta-2 agonist, LABA: long-acting beta-2 agonist, DPI: dry powder inhaler, MDI: metered dose inhaler

* Mann Whitney U

Supplemental Table 4. List of medications.

Brand name ®	Forme	Generic	Posology	Quantity	Pharmaceutical company	Unit Price (€)	R (%)
Ventolin	MDI, suspension for pressurized inhalation	Salbutamol	100 ug	200 doses	GSK	4.14	65
Airomir Autohaler 100 ug	suspension for pressurized inhalation	Salbutamol	100 ug	200 doses	Teva Santé	8.33	65
Bricanyl Turbohaler 500 ug/dose	DPI	Terbutaline	500 ug	100 doses	AstraZeneca	4.67	65
Ventilastin Novolizer 100 ug	DPI	Salbutamol	100 ug	200 doses	MEDAPharma	8.32	65
Ventolin 5 mg/2,5 ml	solution for inhalation via a nebulizer	Salbutamol	5 mg	60 unidoses of 2.5 ml	GSK	17.78	65
Bricanyl 5 mg/2 ml	solution for inhalation via a nebulizer	Terbutaline	5 mg	20 unidoses of 2 ml	AstraZeneca	5.78	65
Atrovent 0,25 mg/ml	solution for inhalation via a nebulizer	Ipratropium Bromure	0.25 mg	30 unidoses of 1 ml	Boehringer Ingelheim	12.14	65
Serevent Diskus 50 ug	MDI, suspension for pressurized inhalation	Salmeterol	50 ug	60 doses	GSK	19.18	65
Serevent 25 ug	DPI	Salmeterol	25 ug	120 doses	GSK	19.18	65
Solupred 20 mg	Orodispersible tablets	Prednisolone	20 mg	20 tablets	Sanofi-Aventis France	3.7	65
Cortancyl 20 mg	scored tablets	Prednisone	20 mg	20 tablets	Sanofi-Aventis France	2.35	65
Cortancyl 5 mg	scored tablets	Prednisone	5 mg	30 tablets	Sanofi-Aventis France	1.84	65
Celestine 2 mg	Orodispersible tablets	Betamethasone	2 mg	20 tablets	MSD France	2.5	65
Flixotide 125 ug	MDI, suspension for pressurized inhalation	fluticasone propionate	125 ug	120 doses	GSK	15.38	65
Flixotide 50 ug	MDI, suspension for pressurized inhalation	fluticasone propionate	50 ug	120 doses	GSK	7.65	65
Flixotide Diskus 100 ug	DPI	fluticasone propionate	100 ug	60 doses	GSK	7.65	65

Flutiform 125 ug/5 ug	MDI, suspension for pressurized inhalation	fluticasone propionate/Formoterol fumarate	125 ug/5 ug	120 doses	MundiPharma	36.25	65
Alvesco 160 ug	MDI, suspension for pressurized inhalation	Ciclesonide	160 ug	60 doses	AstraZeneca	23.42	65
Seretide 250 ug/25 ug	MDI, suspension for pressurized inhalation	fluticasone propionate/Salmeterol	250 ug/25 ug	120 doses	GSK	38.26	65
Seretide 125 ug/25 ug	MDI, suspension for pressurized inhalation	fluticasone propionate/Salmeterol	125 ug/25 ug	120 doses	GSK	34.49	65
Seretide 50 ug/25 ug	MDI, suspension for pressurized inhalation	fluticasone propionate/Salmeterol	50 ug/25 ug	120 doses	GSK	29.83	65
Seretide Diskus 500 ug/50 ug	DPI	fluticasone propionate/Salmeterol	500 ug/50 ug	60 doses	GSK	38.26	65
Seretide Diskus 250 ug/50 ug	DPI	fluticasone propionate/Salmeterol	250 ug/50 ug	60 doses	GSK	34.49	65
Seretide Diskus 100 ug/50 ug	DPI	fluticasone propionate/Salmeterol	100 ug/50 ug	60 doses	GSK	29.83	65
Symbicort Turbuhaler 400 ug/12 ug	DPI	Budesonide/Formoterol fumarate	400 ug/12 ug	60 doses	AstraZeneca	38.26	65
Symbicort Turbuhaler 200 ug/6 ug	DPI	Budesonide/Formoterol fumarate	200 ug/6 ug	120 doses	AstraZeneca	39	65
Innovair 100/6 ug	solution for inhalation	Beclomethasone dipropionate/Formoterol fumarate	100 ug/6 ug	120 doses	Chiesi	34.49	65
Innovair 200/6 ug	solution for inhalation	Beclomethasone dipropionate/Formoterol fumarate	200 ug/6 ug	120 doses	Chiesi	38.23	65
Pulmicort 1 mg/2ml	solution for inhalation via a nebulizer	Budesonide	1 mg	20 unidoses of 2 ml	AstraZeneca	26.91	65
Pulmicort 0,5 mg/2ml	solution for inhalation via a nebulizer	Budesonide	0.5 mg	20 unidoses of 2 ml	AstraZeneca	18.91	65
Beclospin 800 ug/2ml	solution for inhalation via a nebulizer	Beclomethasone dipropionate	800 ug	20 unidoses of 2 ml	Chiesi	30.5	65

Singulair 5mg	Chewable tablet	Montelukast	5 mg	28 tablets	MSD France	22.85	65
Singulair 10mg	Chewable tablet	Montelukast	10 mg	28 tablets	MSD France	22.85	65
Xolair 75 mg	Injectable solution	Omalizumab	75 mg	1 pre-filled syringe of 0.5 ml	Novartis Pharma	183.8	65
Xolair 150 mg	Injectable solution	Omalizumab	150 mg	1 pre-filled syringe of 1 ml	Novartis Pharma	360.99	65
Zithromax 250mg	tablets	Azithromycin	250 mg	6 tablets	Pfizer PFE France	10.7	65
Amoxicilline Biogaran 500mg/5ml	Powder for Oral Solution	Amoxicillin		flacon of 60 ml	Biogaran	1.87	65
Amoxicilline Biogaran 500 mg	capsules	Amoxicillin		12 capsules	Biogaran	1.53	65
Bactrim	oral solution	Sulfamethoxazole/ Trimethoprim	200 mg/40 mg	flacon of 100 ml	Roche	2.07	65
Bactrim Forte	tablets	Sulfamethoxazole/ Trimethoprim	800 mg/160 mg	10 tablets	Roche	1.87	65
Aerius	oral solution	Desloratadine	0.5 mg/ml	flacon of 150 ml	MSD France	2.91	30
Aerius	tablets	Desloratadine	5 mg	30 tablets	MSD France	4.76	30
Wystamm	tablets	Rupatadine	10 mg	30 tablets	Bouchara-Recordati	5.91	30
Zyrtec	oral solution	Cetirizine	0.5 mg/ drop	flacon of 15 ml	UCB Phara SA	2.58	30
Kestin Lyo	oral lyophilizate	Ebastine	10 mg	30 lyophilisates	Almirall SAS	4.22	30
Kestin	tablets	Ebastine	10 mg	30 tablets	Almirall SAS	6.17	30
Cetirizine Biogaran 10mg/ml	oral solution	Cetirizine	0.5 mg/ drop	flacon of 15 ml	Biogaran	2.58	30
Claritin	tablets	Loratadine	10 mg	15 tablets	Bayer Healthcare	2.74	30
Levocetirizine Mylan	tablets	Levocetirizine	5 mg	28 tablets	Mylan Medical SAS	4.14	30
Primalan	oral solution	Mequitazine	2.5ml	flacon of 125 ml	Pierre Fabre Médicament	3.21	30
Xyzall	tablets	Levocetirizine	5 mg	28 tablets	UCB Phara SA	4.71	30
Zatiden	oral solution	Ketotifen	1 mg/5ml	flacon of 150 ml	Alfasigma France	4.46	15
Desloratadine Biogaran	tablets	Desloratadine	5 mg	30 tablets	Biogaran	3.8	30

Rhinomaxil	suspension for nasal spray	Beclomethasone	100 ug	120 doses	Zambon France	6.71	30
Nasonex	suspension for nasal spray	Mometasone furoate	50 ug	120 doses	MSD France	6	30
Rhinoclenil	suspension for nasal spray	Beclomethasone dipropionate	100 ug	120 doses	Chiesi	7.15	30
Avamys	suspension for nasal spray	Fluticasone furoate	27.5 ug	120 doses	GSK	6	30
Flixonase	nasal solution	Fluticasone propionate	50 ug	120 doses	GSK	6	30
Nasacort	suspension for nasal spray	Triamcinolone acetonide	55 ug	120 doses	Sanofi-Aventis France	8.11	30
Allergodil	suspension for nasal spray	Azelastine	0.127 ug	120 doses	Mylan Medical SAS	7.57	30
Pivalone 1% nasal solution	nasal solution	Tixocortol pivalate	1 g for 100 g	100 doses, flacon of 10 ml	Pfizer PFE France	2.42	30
Dymista 137 ug/50 ug	nasal solution	Azelastine/Fluticasone propionate	125 ug/50 ug	120 doses	Mylan Medical SAS	15.47	30
Allergodil 0.05%	eye drop	Azelastine chlorhydrate	50 mg for 100 ml	flacon of 6 ml	Mylan Medical SAS	5.1	30
Naabak 19.6 mg/0.4 ml	eye drop	Acide spaglumique	19.6 mg	36 unidoses of 0.4 ml	Théa Pharma	4.16	30
Opticron 2%	eye drop	Cromoglicate de sodium	2 gr for 100 ml	24 unidoses of 0.35 ml	Coopération Pharmaceutique Française	2.8	30
Chromedil 2%	eye drop	Cromoglicate de sodium	2 gr for 100 ml	30 unidoses of 0.3 ml	Europhta	3.49	30
Zalerg	eye drop	Ketotifen	25 mg for 100 ml	30 unidoses of 0.4 ml	Théa Pharma	3.49	30
Lévofree	eyedrop	Levocabastine	0.5 mg/ml	30 unidoses of 0.3 ml	Chauvin SA	3.49	30
Jext	Injectable solution IM	Adrenaline	150 ug <i>or</i> 300 ug	2 pre-filled pencils of 0.15 ml each	ALK Abello	66.23	65
Epipen 0.15 mg/0.3ml	Injectable solution IM	Adrenaline	150 ug	1 pre-filled pencil of 2 ml	MEDAPharma	73.35	65
Epipen 0.30 mg/0.3ml	Injectable solution IM	Adrenaline	300 ug	1 pre-filled pencil of 2 ml	MEDAPharma	73.35	65

Anapen 0.15 mg/0.3ml	Injectable solution IM	Adrenaline	150 ug	2 pre-filled syringes of 1 ml each	Bioproject Pharma	66.23	65
Anapen 0.30 mg/0.3ml	Injectable solution IM	Adrenaline	300 ug	2 pre-filled syringes of 1 ml each	Bioproject Pharma	66.23	65
Emerade	Injectable solution IM	Adrenaline	150 ug or 300 ug	2 pre-filled pencils	Chauvin SA	64.63	65
Emerade	Injectable solution IM	Adrenaline	500 ug	2 pre-filled pencils	Chauvin SA	66.91	65
Ranitidine Arrow 300 mg	Effervescent tablets	Ranitidine	300 mg	14 tablets	Arrow Générique	7.11	15
Inexium 20 mg	tablets	Esomeprazole	20 mg	14 tablets	AstraZeneca	4.08	65
Inexium 20 mg	tablets	Esomeprazole	20 mg	28 tablets	AstraZeneca	8.2	65
Ogastoro 15 mg	Orodispersible tablets	Lansoprazole	15 mg	28 tablets	Takeda France	8.2	65
Ogastoro 30 mg	Orodispersible tablets	Lansoprazole	30 mg	28 tablets	Takeda France	8.57	65
Mopral 20 mg	capsules	Omeprazole	20 mg	28 tablets	AstraZeneca	8.57	65
VAXIGRIP TETRA	Influenza vaccine, Injectable solution IM or SC			1 pre-filled syringe	Laboratoire Sanofi Pasteur Europe	10.11	100

R : reimbursement, DPI : dry powder inhaler, MDI : metered dose inhaler, GSK : GlaxoSmithKline, IM : intramuscular, SC : subcutaneous