AstraZeneca

STUDY REPORT SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: Pulmicort Respules
ACTIVE INGREDIENT: Budesonide

Study No: NCT01232322

Developmental Phase: post-marketing
Study Completion Date: July 2011
Date of Report: January 2013

OBJECTIVES:

The purpose of this study is to investigate the safety and efficacy for long term treatment of the drug in children aged 6 months and < 5 years on bronchial asthma in daily clinical usage.

METHODS: Observational Study

RESULTS:

In order to grasp the safety and efficacy of Pulmicort Respules under actual long-term use in infants with bronchial asthma (age: >=6 months, < 5 years), this investigation was conducted from Oct 2006 to Dec 2010 (observation period: 3 years) by central registration method with the target number of case reporting forms to collect as 400. As the result, 625 case reporting forms were collected. The summary of review result about 620 safety and efficacy evaluable patients is as follows:

Continuation or discontinuation of Pulmicort Respules

Regarding 620 safety evaluable patients, the drug was continued for more than six months in 77.3 % (479 patients), for more than one year in 60.2 % (373 patients), for more than two years in 38.4 % (238 patients), and for more than three years in 23.2 % (144 patients).

The number of patients who stopped the drug was 457 in total (73.7 %: 457/620 patients). The most common reason of withdrawal was ‘improvement of asthma symptoms’ for 220 patients (48.1 %), followed by ‘no revisit' for 140 patients (30.6 %), ‘others (decision or

request by the parents, the patient was reluctant, etc)' for 89 patients (19.5 %), 'adverse event' for six patients (1.3 %), and 'lack of effect' for two patients (0.4 %).

Safety

1) Adverse drug reaction (ADR) events were reported for 52 of 620 safety evaluable patients (8.4 %). The major ADRs were 'infection and infestations' such as bronchitis and 'respiratory, thoracic, and mediastinal disorders' such as asthma and upper respiratory tract inflammation.
2) ADRs developed more than two years after the drug was started were reported for six patients (12 events). No increase of frequency was recognized for adrenal function related ADRs, which were concerns about long-term use of the drug.
3) As the result of review of the ADR cumulative incidence rate by patient's background factors, treatment factors, and factors about the drug, the rate was higher in patients with history of systemic steroid than those without ($p=0.008$). However, since attention has been attracted for decreasing and withdrawal of systemic steroid by the description in '2.Important precautions' of the Precautions for use in label, no new measures should be taken.
4) As the result of review of the serious AE cumulative incidence rate by patient's background factors, treatment factors, and factors about the drug, significant differences between categories were recognized for the groups by start age of the drug treatment, inpatient/outpatient, disease type, baseline severity, with/without concomitant disease, duration of illness, and with/without history of systemic steroid ($p<0.05$). As the result of reviewing these factors, it was decided that there should be no need to take any measures.
5) There was no safety problem with using mesh nebulizer, tuner, or face mask.
6) The cases of switching to other inhalation steroid during six weeks after withdrawal of Pulmicort Respules were reviewed. The number of patients who switched the drug under actual drug use was small as 11.0 % (35/317 patients), indicating no specific problem.

Key investigation item:

1) Height and weight after treatment with Pulmicort Respules were examined using Standard Deviation Score (hereinafter referred to as SDS) as an index. As the result, SDSs of height and weight increased from the baseline at every observation period. As the result of comparison with the standard growth curve of Japanese children by sex, no harmful effect on growth was confirmed after administration of Pulmicort Respules.
2) Regarding 620 safety evaluable patients, as adrenal function related ADR, 'Adrenal insufficiency' in two patients (0.3 %), 'Blood cortisol decreased' in two patients (0.3 %), 'Adrenal disorder' in one patient (0.2 %), and 'Blood corticotrophin decreased' in one patient (0.2 %) were reported. However, no clinical symptoms or signs were recognized with decrease or increase of cortisol or decrease of blood corticotrophin.

   The variation of cortisol from the baseline in each observation period showed mild decrease for all periods except two years and six months with the drug.

However, the mean cortisol value was within the common reference range (>= 4 mcg/dL).

As to the effects on adrenal function, no new measures should be taken since it has been included in the Important Precautions of the Precautions for use to attract attention.

3) Infections (AE) were confirmed in 368 of 620 safety evaluable patients (59.4 %). The main events were bronchitis in 189 patients (30.5 %), pharyngitis in 115 patients (18.5 %), gastroenteritis in 96 patients (15.5 %), influenza in 83 patients (13.4 %), pneumonia in 46 patients (7.4 %), varicella in 40 patients (6.5 %), and upper respiratory tract inflammation in 175 patients (28.2 %).

   As the result of review of the cumulative incidence rate of infections as AE by the patient's background factors, treatment factors, and factors about the drug, significant differences between categories were recognized for the groups by start age of the drug treatment, baseline severity, with/without past medical history, with/without concomitant disease, with/without concomitant drug(s), with/without therapeutic drug of bronchial asthma, with/without drug mixture, with/without using face mask, and maximum daily dose ($p < 0.05$). As the result of reviewing these factors, it was decided that there should be no need to take any measures.

4) Regarding ADR/infections cumulative incidence rate in 620 safety evaluable patients, no significant difference was recognized for the ADR cumulative incidence rate by maximum daily dose ($p = 1.000$).

Efficacy

1) Regarding the final overall treatment evaluation, moderate or higher level of improvement was confirmed in 568 of 620 efficacy evaluable patients (91.6 %). Regarding the final overall treatment evaluation for each observation period, moderate or higher level of improvement was confirmed in around 90 %, presenting successful results.
2) The rate of patients with improvement by the final overall treatment evaluation was reviewed by patient’s background factors, treatment factors, and factors concerning Pulmicort Respules to identify the factor having impact on the final overall treatment evaluation. As the result, significant differences between categories were recognized for the groups by with/without past medical history, with/without concomitant drug(s), with/without therapeutic drug of bronchial asthma, with/without using face mask, and the maximum daily dose ($p < 0.05$). However, there was no item requiring any specific measures.
3) Clinical course (frequency of asthmatic attack, degree of asthmatic attack, daily life, and night sleep) was reviewed for the 620 efficacy evaluable patients. As the result, successful data were confirmed for each clinical course.

As stated above, regarding the safety and efficacy of Pulmicort Respules in long-term use, no problem requiring any new specific measures was confirmed in the SCEI for long-term use.