Fixed combinations of corticosteroids and long-acting beta-2-receptor agonists for inhaled use in patients with asthma

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Fixed combinations of corticosteroids and long-acting beta-2-receptor agonists for inhaled use in patients with asthma

Executive summary

Background

The Federal Joint Committee commissioned the Institute for Quality and Efficiency in Health Care to evaluate the benefits and harms of fixed combinations of inhaled corticosteroids (ICS) and inhaled long-acting beta-2-receptor agonists (LABA) in patients with asthma. The drugs to be evaluated were those approved in Germany at the time of the start of the project (07/2005).

Research question

The aims of the present investigation were:

- the evaluation of the benefits and harms of formoterol/budesonide administered by a fixed combination inhaler compared with formoterol and budesonide administered by separate inhalers in patients with asthma.
- the evaluation of the benefits and harms of salmeterol/fluticasone administered by a fixed combination inhaler compared with salmeterol and fluticasone administered by separate inhalers in patients with asthma.
- the evaluation of the benefits and harms of formoterol/budesonide administered by a fixed combination inhaler compared with salmeterol/fluticasone administered by a fixed combination inhaler.

The focus of the evaluation was on patient-relevant therapy goals.

The evaluation was conducted on the basis of the comparison and weighing of desired and undesired effects of the individual treatment regimens (weighing of benefits and harms).

The evaluation considered the fixed combinations approved in Germany at the start of the project (7/2005) with their valid approval status at this time point. The fixed combination of formoterol/beclometasone dipropionate, which was approved in July 2006, was not included in the evaluation. The extension of the approval for the fixed combination of
formoterol/budesonide as reliever therapy (issued in December 2006), was also not considered in the present evaluation. This new approval and extended approval will be evaluated in an additional project. Subsequently, the evaluations will be merged.

**Methods**

A systematic literature search was performed in the databases MEDLINE (1966 to July 2006), EMBASE (1980 to July 2006), and CENTRAL (July 2006). In addition, reference lists of relevant secondary publications (systematic reviews, HTA reports), trial registries as well as publicly accessible drug approval documents were screened. Furthermore, the manufacturers of fixed combinations approved in Germany were asked to provide information on relevant published or unpublished trials. Finally, in January/February 2007, information on further trials relevant to the topic under investigation was requested within the framework of the submission of comments on the preliminary version of the report (preliminary report).

Randomised controlled trials (RCTs) in patients with asthma were included that compared formoterol/budesonide (FORM/BUD) or salmeterol/fluticasone (SALM/FLU) administered by a fixed combination inhaler with formoterol and budesonide (FORM+BUD) or salmeterol and fluticasone (SALM+FLU) administered by separate inhalers. The minimum study duration was 12 weeks. Direct comparative RCTs investigating both fixed combinations were also included.

The literature screening was performed by 2 reviewers independently of one another.

After an evaluation of study quality, the results of the individual trials were collated according to therapy comparisons and outcomes. Meta-analyses of the data were not performed due to the heterogeneity of study designs.

IQWiG’s preliminary evaluation, the preliminary report, was published on the Internet (www.iqwig.de) and interested persons and parties were asked to submit comments.

**Results**

The literature search identified 11 trials for the evaluation of the fixed combinations of LABA/ICS (thereof 1 trial in children). Four trials compared FORM/BUD versus FORM+BUD, and 4 trials compared SALM/FLU versus SALM+FLU (1 trial in children). Three trials investigating direct comparisons of fixed combinations were identified. Of the
trials included, 6 showed no deficiencies, 1 showed minor deficiencies, and 4 showed major deficiencies regarding study and publication quality.

The drugs were administered by identical inhaling systems in all trials comparing LABA/ICS versus LABA+ICS (Turbohaler® for formoterol and budesonide; Diskus® for salmeterol and fluticasone). No trials were identified that applied different inhaling systems in the comparator groups. In all trials comparing fixed combinations with each other, FORM/BUD was administered by Turbohaler® and SALM/FLU was administered by Diskus®.

The following table provides an overview of the patient-relevant outcomes investigated in the trials included.

Table 1: Overview of the patient-relevant outcomes in the trials included

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* a: The publications Rosenhall 2003a+b refer to a 6-month continuation performed by the Swedish study centres participating in the trial by Rosenhall 2002.
* b: No direct assessment of asthma symptoms, but an assessment of the use of reliever medication or of the ACQ (Asthma Control Questionnaire); these data were only presented as supplementary information.

Data that allow an evaluation of the therapy goal “maintenance and improvement of physical capacity” were not collected in the trials. In respect of their design and duration, none of the trials included was designed to investigate the effect of the assessed drugs on asthma-related mortality or overall mortality. No evidence of a benefit of LABA/ICS fixed combinations is therefore available for these parameters.
A direct assessment of asthma symptoms was performed in the trials by Jenkins 2006 and Zetterström 2001. In these trials, asthma symptoms improved in both treatment groups. In Jenkins 2006, the proportion of symptom-free days during treatment with FORM/BUD or FORM+BUD compared with previous medication increased by 31% and 32% respectively. In Zetterström 2001, the proportion of symptom-free days under FORM/BUD and FORM+BUD increased by 25% and 22% respectively; the proportion of asthma-related nocturnal awakenings decreased by 8% (FORM/BUD) and by 6% (FORM+BUD) (in each case, compared with previous medication).

In Rosenhall 2002, asthma symptoms were assessed with the Asthma Control Questionnaire (ACQ). The ACQ score, which, besides asthma symptoms (5 items), also covers the use of reliever medication (1 item) as well as lung function (1 item), improved by about 0.5 points both under treatment with FORM/BUD and FORM+BUD (range of scale: 0-6).

In summary, the study results can be seen as an indication that the reduction in asthma symptoms using either a fixed combination inhaler or separate inhalers is comparable.

Asthma exacerbations

In Jenkins 2006, more patients taking FORM+BUD reported a mild exacerbation than those taking FORM/BUD (51% vs. 45%). This difference was not statistically significant. In Zetterström 2001, the proportion of patients with mild exacerbations was the same in both groups (about 40%).

In Zetterström 2001, the proportion of patients with severe exacerbations was slightly higher under FORM+BUD (9.6%) than under FORM/BUD (6.5%); the difference was not statistically significant. In Rosenhall 2002, the proportion of patients with severe exacerbations was comparable between treatment groups (FORM/BUD: 15%; FORM+BUD: 14%).

Therefore, the trials do not provide evidence of different exacerbation rates under treatment with FORM/BUD compared with FORM+BUD.

Hospital admissions and outpatient visits

In Rosenhall 2003a+b, the group receiving FORM+BUD showed higher mean values regarding visits to an emergency unit (0.34 visits/patient/12 months) and outpatient visits
(0.42 visits/patient/12 months) than the group receiving FORM/BUD (0.10 and 0.27 visits/patient/12 months). However, these rates, expressed as the mean number of events per person in 12 months, were very low in both groups (<1 event per person per 12 months). The relevance of the observed differences is unclear; statistical significance was not tested. The results cannot be assessed as evidence of a difference between FORM/BUD and FORM+BUD.

**Adverse effects**

In the 4 trials investigated, no differences were shown regarding the frequency and type of adverse events between the 2 forms of administration (FORM/BUD and FORM+BUD).

**Health-related quality of life**

In both treatment groups, an increase in the total score by about 0.5 points was reported in the disease-specific quality of life questionnaire MiniAQLQ (range of scale: 0-7). The improvements in the scores of the individual domains of the questionnaire were also comparable between groups. A difference in the quality of life of patients treated with FORM/BUD or FORM+BUD can therefore not be inferred from the trials.

**Salmeterol/fluticasone versus salmeterol+fluticasone**

**Asthma symptoms**

The proportion of patients with symptom-free days or nights increased in all trials, both under SALM/FLU as well as under SALM+FLU. In general, the results of both forms of administration were comparable. A numerical (statistically non-significant) advantage of SALM/FLU versus SALM+FLU in respect of symptom-free nights (33% vs. 26% of patients), as seen in Chapman 1999, was not shown in the other trials. In the paediatric trial (van den Berg 2000), the results between patients receiving SALM/FLU and SALM+FLU were also comparable.

In summary, the trials do not provide evidence of an advantage of either form of administration regarding the reduction in asthma symptoms.

**Hospital admissions and outpatient visits**

In Aubier 1999, outside the study visits, most patients did not need asthma-related medical care (SALM/FLU: 66% of patients; SALM+FLU: 68%). The proportion of patients who received additional medical treatment was comparable between both groups. The number of
outpatient visits and the number of patients admitted to hospital were also comparable (hospital admissions: SALM/FLU vs. SALM+FLU; 4 patients vs. 6 patients).

Adverse effects

No trials showed clinically relevant or statistically significant differences regarding the frequency and type of adverse events.

Activities of daily living

In Aubier 1999, about 25% of patients in both treatment groups had to interrupt work or other activities because of asthma symptoms. For most of the affected patients, this interruption of daily activities lasted less than an hour. More than half of the patients had to work or perform other main activities whilst being affected by asthma symptoms; this impairment lasted 4 hours or longer in about 20% of patients.

The asthma-related impairment in activities of daily living was comparable between SALM/FLU and SALM+FLU; i.e. there was no advantage for either the use of a fixed combination inhaler or separate inhalers.

Treatment satisfaction

In Aubier 1999, at study entry, most patients were satisfied or very satisfied with their previous medication (74% and 64% of patients who were later randomised to the SALM/FLU and SALM+FLU groups). At the end of study, the proportion of patients who were satisfied or very satisfied had increased to 81% (SALM/FLU) and 79% (SALM+FLU). Treatment satisfaction at the end of study was therefore comparable between groups.

In this double-blind, double-dummy trial, a possible advantage of the use of a single inhaler in the SALM/FLU group compared with the use of 2 inhalers in the SALM+FLU group could not be perceived. Patient satisfaction therefore referred to the treatment effect and not to the handling of the medication. The impact of the differences in the handling of the medication could not be investigated in this trial.

Formoterol/budesonide versus salmeterol/fluticasone

Asthma symptoms

Asthma symptoms were reduced in all trials in both the FORM/BUD and in the SALM/FLU group. The asthma symptom scores at the end of the trials were comparable between groups.
In the SAM40040 2004 trial, the proportion of patients with $> 75\% \leq 100\%$ symptom-free days throughout the whole course of the trial was 40% in both groups. In each group, 58% of patients were $> 75\% - \leq 100\%$ symptom-free at night throughout the trial. Regarding the effect on asthma symptoms, the trials therefore did not show a difference between the fixed combinations of FORM/BUD and SALM/FLU.

**Asthma exacerbations**

In Aalbers 2004, the mean exacerbation rate was comparable between treatment groups (FORM/BUD: 0.036/month; SALM/FLU: 0.041/month). Likewise, in the SAM40040 2004 trial, no difference between both fixed combinations was shown regarding the mean exacerbation rate (FORM/BUD: 3.07/24 weeks; SALM/FLU: 3.06/24 weeks), the number of exacerbations per patient, the severity of exacerbations, as well as the length of time to the first exacerbation.

**Hospital admissions and outpatient visits**

Data on the utilisation of outpatient and inpatient services were only collected in the SAM40040 2004 trial. Regarding outpatient visits (including visits to emergency units), both the number of affected patients and the absolute number of visits was comparable between both fixed combinations. Regarding the use of inpatient services, the absolute risks under the fixed combination of SALM/FLU were numerically higher than under the fixed combination of FORM/BUD (referral to hospital: 0.1% vs. 0.7%; stay in an intensive care unit: 0% vs. 0.3%; stay in a general ward: 0.1% vs. 0.6%). However, the overall number of observed cases was very small and the 95% confidence intervals of the risks overlapped. In summary, no differences between both fixed combinations regarding hospital admissions and outpatient visits can be shown with this trial.

**Adverse effects**

No noticeable differences between both fixed combinations were shown regarding the overall adverse event rate as well as the rate of study discontinuations due to adverse events. In Aalbers 2004, the serious adverse event rate was higher in the FORM/BUD group than in the SALM/FLU group (5% vs. 2%; 11 vs. 5 patients). In the SAM40040 2004 trial, the absolute number of serious adverse events was higher under SALM/FLU than under FORM/BUD (29 events in 20 [3%] patients vs. 13 events in 12 [2%] patients). The relevance of the observed differences is unclear. In summary, no differences in adverse events between fixed combinations of FORM/BUD and SALM/FLU can be inferred from these results.
Conclusion

**Adolescents and adults**

- In adolescents and adults, no evidence of an additional benefit is available for the administration of formoterol/budesonide in a fixed combination inhaler compared with the administration of formoterol and budesonide in separate inhalers (or vice versa) regarding patient-relevant therapy goals. In fact, when applying the same inhaling system (Turbohaler®), the trials on formoterol and budesonide provide similar results for fixed combination inhalers and separate inhalers.

- In adolescents and adults, no evidence of an additional benefit is available for the administration of salmeterol/fluticasone in a fixed combination inhaler compared with the administration of salmeterol and fluticasone in separate inhalers (or vice versa) regarding patient-relevant therapy goals. In fact, when applying the same inhaling system (Diskus®), the trials on salmeterol and fluticasone also provide similar results for fixed combination inhalers and separate inhalers.

- In adolescents and adults, no evidence of a difference in benefit is available between the fixed combinations of formoterol/budesonide versus salmeterol/fluticasone. Overall, the trials provide similar results regarding the use of both fixed combinations (when applying Turbohaler® or Diskus®).

**Children**

- Data in children were only available for the comparison between salmeterol/fluticasone administered by a fixed combination inhaler and salmeterol and fluticasone administered by separate inhalers (1 trial). This trial did not provide evidence of a difference between the two different forms of administration of salmeterol and fluticasone.

- Due to the lack of data, no statement can be made on the comparison between formoterol/budesonide administered by a fixed combination inhaler versus formoterol and budesonide administered by separate inhalers in children.

**Key words:** asthma, long-acting beta-2-receptor agonists, glucocorticosteroids, combination drugs, fixed combinations, systematic review