

Asthma medication: How do fixed combinations of inhaled steroids and long-acting beta-2-agonists compare to combinations of the same drugs taken



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Asthma is a lung disease in which the airways (bronchi) are always more prone to inflammation. In people who have asthma, the muscles surrounding the airways tend to contract or squeeze more. Together, these things make their airways narrower. Controller medication is taken regularly to try to prevent severe breathing difficulties by reducing the inflammation and narrowing of the airways. It is taken every day to keep asthma under control in the long term. Controller medications include the so-called corticosteroids, often simply referred to as steroids, and the long-acting beta-2-agonists (LABAs). They keep asthma under control by fighting the underlying inflammation in the lungs and relaxing the muscles of the airways.

Using fixed combinations of drugs

For many years now, combinations of steroids and LABAs have been used in the treatment of asthma. LABAs are used in addition to steroids if moderate or severe asthma cannot be kept under control with steroids alone. They are usually inhaled (breathed into the lungs using an inhaler device or “puffer”) so that they can work directly at the site where the airways are inflamed and narrowed. The exact dose and way in which the medication is taken depends on the type and severity of symptoms and how old the patient is.

Because their effect lasts up to 12 hours, LABAs only need to be taken once or twice a day in order to keep the asthma in check. LABAs should always be taken together with steroids, because they may be harmful otherwise. Research suggests that controller therapy with LABAs alone could lead to life-threatening asthma attacks.

In the past, people with asthma had to use two different inhalers – one containing a steroid, the other containing a LABA – and the two drugs were inhaled separately. For years now, inhalers which deliver both drugs at the same time have been available. This kind of treatment, with fixed amounts of two or more drugs, is known as a fixed combination. Three fixed combinations of drugs are currently licensed in Germany for use in the long-term treatment of asthma: budesonide (steroid) and formoterol, fluticasone (steroid) and salmeterol, as well as beclomethasone (steroid) and formoterol. The combination of budesonide and formoterol has now also been licensed for use as relief medication, so it can be used to treat acute

asthma attacks too.

How effective are fixed combinations?

The German Institute for Quality and Efficiency in Health Care (IQWiG) wanted to know whether the various drugs have a different effect depending on whether they are taken as a fixed combination or separately. The IQWiG researchers looked for trials which compared the effect of taking the first two above-mentioned fixed combinations with the effect of taking a combination of the same drugs separately. They also looked for trials which directly compared the fixed combinations with each other. The approval status of this group of drugs has changed since July 2006. IQWiG has now updated its original evaluation of the fixed combination trials and analysed new trials that were published in the autumn of 2008.

The people who participated in these trials agreed to be randomly allocated to one of (at least) two groups. The participants in one group used the fixed combination, whereas those in the other group took a combination of the two drugs separately. In the trials which compared the different fixed combinations with each other, each group of participants used one of these fixed combinations.

The IQWiG researchers found a total of 16 relevant trials involving mainly adults and teenagers. Of those trials, five compared the fixed combination of budesonide and formoterol with combinations of these drugs taken separately. Four trials compared the fixed and separate combinations of fluticasone and salmeterol. For each of these two fixed combinations, there was one trial that also looked at the effects in children. No trials have compared the effect of the newly approved fixed combination of beclomethasone and formoterol with the effect of inhaling these drugs separately.

Seven trials directly compared different fixed combinations with each other. Five of these compared the fixed budesonide/formoterol combination with the fixed fluticasone/salmeterol combination, one compared beclomethasone/formoterol with budesonide/formoterol, and one compared beclomethasone/formoterol with fluticasone/salmeterol.

When looking at the trials, the IQWiG researchers wanted to see whether the different treatment options had different effects on certain important factors, such as how frequently the people had asthma attacks and how often they had to go to hospital or see a doctor. They were also

interested in adverse effects, the patients' quality of life, and their satisfaction with treatment.

What they found

After evaluating all the trials, the researchers concluded that, in teenagers and adults, there is no overall difference between taking fixed or separate combinations of budesonide/formoterol or fluticasone/salmeterol in terms of, for example, their effect on asthma symptoms. They did not find any trials comparing the fixed beclomethasone/formoterol combination with a combination of these drugs taken separately.

When compared directly, the effects that the different fixed combinations had on asthma symptoms were also very similar. There were no differences between the adverse effects of the drugs in these trials when used for the long-term treatment of asthma.

The fixed combination of budesonide and formoterol has now also been approved for use as relief medication in the treatment of asthma. Its use in this way has only been tested in one trial, where it was compared with individually adapted fixed combinations of fluticasone and salmeterol.

The results of this trial suggested that the fixed combination of budesonide and formoterol was possibly somewhat more effective at preventing serious asthma attacks. But the IQWiG researchers pointed out that this conclusion should be interpreted with caution because they are not sure whether they had access to all of the relevant trials of this treatment. The manufacturer was not prepared to supply IQWiG with a list of all the studies done in this area. It is therefore not clear whether or not future research will confirm that the fixed combination of budesonide and formoterol has advantages in the acute and long-term treatment of asthma.

The two trials that looked at the effect of taking fixed or free combinations in children (one trial of fluticasone/salmeterol and one trial of budesonide/formoterol) did not show a clear difference between the two ways of taking the drugs. It is not possible to say whether it makes a difference if children use one or two inhalers to take beclomethasone and formoterol, as no appropriate trials have looked into this.

There is not enough good research data to be able to say how the drugs affect people's physical fitness or how long they live.

One commonly claimed advantage of fixed combinations is that they make it easier for people to take their medication and therefore increase the likelihood that they will take it regularly. It is assumed that this improves the outcome of treatment. However, none of the trials looked into this question, so it is not clear whether this assumption is true.

Review on LABAs published by US regulatory authority (FDA)

In February 2010, the US regulatory authority FDA (Food and Drug Administration) published an analysis of studies in which patients used LABAs. The FDA concluded that using LABAs can make asthma symptoms worse and lead to more hospital stays. This is particularly true when these drugs are used alone, but also when they are used together with steroids in a fixed combination.

Because of these findings, the FDA once again stressed that LABAs should only be used in combination with steroids. If children or teenagers have to take them, they are to be used in the form of a fixed combination. Generally speaking, LABAs should only be considered if someone has already tried out a controller medication (such as a steroid) on its own and that has not helped enough. For this reason, the researchers at the FDA pointed out that fixed combinations should only be used for a limited time, and that people should switch to treatment without LABAs wherever possible. According to the FDA review, there is not enough research to be able to say how safe fixed combinations are, so more safety studies are needed.

This additional information has been provided by the U.S. National Library of Medicine:

In the U.S., a fixed combination of the drugs beclomethasone and formoterol is not available, and the Food and Drug Administration (FDA) has not licensed the use of a fixed combination of budesonide and formoterol to treat acute asthma attacks.

Author: German Institute for Quality and Efficiency in Health Care (IQWiG)

Note

This health information is a summary of a scientific report

published by IQWiG. It is not an assessment of the right to have health care services reimbursed by statutory health insurance funds in Germany. By law, decisions about the reimbursement of diagnostic and therapeutic procedures can only be made by the German Federal Joint Committee (G-BA). The Federal Joint Committee takes IQWiG reports into consideration in its decision-making process. You can find information about the decisions of the German Federal Joint Committee on its English-language website, www.english.g-ba.de (URL: <http://www.english.g-ba.de/>) .

Glossary

asthma

Asthma (asthma bronchiale) is a permanent (chronic) disease with symptoms like coughing and breathlessness often occurring in acute attacks. In asthma, the airways are overly sensitive. The development of asthma is often associated with an overreaction to foreign substances or physical stimuli, frequently in connection with an allergy.

bronchi

The air we breathe in enters the lungs through the windpipe. From there it is conducted through the branching structure of airways (bronchi), which become finer and finer, to the pulmonary vesicles (alveoli). The exchange between oxygen and carbon dioxide takes place in the alveoli.

inflammation

An inflammation is a (defense) reaction of the body to an injury, irritation or infection. More blood is brought to the respective body part to protect the body. This is why this body part feels warmer, becomes swollen and red and is usually more sensitive. If the inflammation affects the mucous membranes, they secrete more fluid than usual. This helps to wash out the germs that have entered.

Sources

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