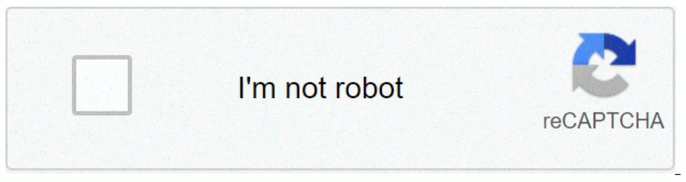

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Budesonide formoterol fumarate

SYMBICORT combines an ICS, budesonide and a LABA medicine, formoterol. LABA drugs, such as formoterol, when used alone can increase the risk of hospitalization and death from asthma problems. When an ICS and LABA are used together, this risk is not significantly increased Do not use SYMBICORT for sudden severe symptoms of COPD or asthma Before using SYMBICORT, tell your healthcare professional about all your medical conditions, including if you have heart conditions or hypertension, and all medications you may take. Some patients taking SYMBICORT may experience an increase in blood pressure, heart rate, or change in heart rhythm Do not use SYMBICORT more often than prescribed. SYMBICORT should be taken as 2 puffs 2 times a day While taking SYMBICORT, do not use another medicine containing a LABA for any reason. Ask your healthcare professional or pharmacist if any of your other drugs are LABA drugs Call your healthcare professional or get medical care right away if: Your respiratory problems get worse You need to use the rescue inhaler more often than usual or the rescue inhaler does not work as well to relieve symbicort symptoms can cause serious side effects , including: Using too much of a LABA drug can cause chest pain, fast and irregular heartbeat, tremor, increased blood pressure, headache or nervousness Fungal infection in the mouth or throat (thrush). Rinse mouth with water without swallowing after using SYMBICORT to reduce the chance of getting thrush pneumonia and other lower respiratory tract infections. People with COPD may be more likely to have pneumonia and other lung infections. ICS can increase the chance of getting pneumonia. Call your healthcare professional if you notice any of the following symptoms: increased mucus production or color change, fever, increased cough, chills, or increased respiratory problems Effects of the immune system and an increased likelihood of infections. Tell your healthcare professional about any signs of infection such as: fever, body pain, feeling tired, vomiting, pain, chills or surrenal nausea. This can happen when you stop taking oral corticosteroid drugs and start inalated corticosteroid medicine Hissing increase immediately after taking SYMBICORT. Always have a rescue inhaler with you to treat sudden severe allergic reactions including rash, hives, swelling of the face, mouth and tongue, and respiratory problems. Call your healthcare professional or get emergency medical care if you get any symptoms of a severe allergic reaction Low bone mineral density happen in people who have a high probability of low bone mineral density (osteoporosis) slowed growth in children. The growth of a child should be checked regularly during the use of SYMBICORT eye problems including glaucoma and cataracts. You should have regular eye exams while using SYMBICORT swelling of blood vessels. This can happen in people with asthma. Tell your healthcare professional immediately if you have: a of noses and needles or numbness of the arms or legs, rash, flu-like symptoms, or pain and swelling of the nasal sinuses Decreases in potassium levels in the blood (low blood) Increases in blood sugar levels (hyperglycaemia) The most common side effects of SYMBICORT include: COPD: throat irritation, thrush in the mouth and throat, bronchitis, sinusitis and upper respiratory infections headaches, upper respiratory tract infection, throat pain, sinusitis, flu, back pain, nasal congestion, stomach pain, vomiting and thrush in the mouth and throat COPD: SYMBICORT 160/4.5 mcg is used in the long term to improve the symptoms of chronic obstructive bronchina (COPD), including chronic bronchitis and emphysema, for better breathing and less flare-up. Asthma: SYMBICORT is for the treatment of asthma in patients of 6 years and older whose asthma is not well controlled with an asthma control drug such as an inhaled corticosteroid (ICS) or whose asthma guarantees treatment with both an ICS and a long-term beta-adrenergic agonist (LABA). SYMBICORT is not used to relieve sudden respiratory problems and will not replace a rescue inhaler. You can report side effects related to Astra-eneca products by clicking here. SYMBICORT contains both budesonide and formoterol; therefore, the following action mechanisms for individual components apply to SYMBICORT. These drugs represent two classes of drugs (a synthetic corticosteroid and a long-term selective beta-adrenocetor agonist) that have different effects on the clinical, physiological and inflammatory indices of COPD and asthma. Budesonide Budesonide is an anti-inflammatory corticosteroid that shows powerful glucocorticoid activity and weak mineracocorticoid activity. In standard in vitro and animal models, budesonide has about 200 times greater affinity for the glucocorticoid receptor and a topical anti-inflammatory potency 1000 times higher than cortisol (rat croton oil ear edema assay). As a measure of systemic activity, budesonide is 40 times more potent than cortisol when administered subcutaneously and 25 times more powerful when administered orally in the rat thymus involution assurable. In glucocorticoid receptor affinity studies, the 22R form of budesonide was twice as active as epimera 22S. In vitro studies have indicated that the two forms of budesonide will not interconvert. Inflammation is an important component in the pathogeneases of COPD and asthma. Corticosteroids have a wide range of inhibitory activities against multiple types of cells (e.g., mastocytes, eosinophils, neutrophils, macrophages and lymphocytes) and mediators (e.g., histamine, eicosanoids, leucorienes and cytokines) involved in allergic and non-allergic inflammations. These anti-inflammatory actions of can contribute to their effectiveness in COPD and asthma. Studies in asthmatic patients have shown a favourable relationship between peddled anti-inflammatory activity and effects on a wide range of doses of budesonide. This is explained by a combination of a relatively high local anti-inflammatory effect, extensive liver degradation of the first step of the oral absorbed drug (85%-95%) and the low power of the metabolites formed. Formoterol Formoterol fumarate is a selective beta-adrenergic agonist with long-acting action (beta2-agonist) with a rapid onset of action. The smoker of inhaled formoterol acts locally in the lung as a bronchodylator. In vitro studies have shown that formoterol has more than 200 times more beta2-receptor agonist activity than beta1receptors. In vitro binding selectivity at beta2-over beta1-adrenoceptors is higher for formoterol than for albuterol (5 times), while salmeterol has a higher beta2-selectivity ratio (3 times) than formoterol. Although beta2-receptors are the predominant adrenergic receptors in smooth bronchial muscle and beta1receptors are the predominant receptors in the heart, there are also beta2-receptors in the human heart that includes 10% to 50% of the total beta-adrenergic receptor. The precise function of these receptors has not been established, but they raise the possibility that even highly selective beta2-agonists may have heart effects. The pharmacological effects of beta2-adrenocetor agonistic drugs, including formoterol, are at least partly attributable to stimulation of intracellular adenyl cyclic, the enzyme that catalzes the conversion of adenosine tripphosphate (ATP) to cyclic-3', adenosine monophosphate (cyclic AMP). Increased levels of cyclic AMP cause bronchial smooth muscle relaxation and inhibition of the release of immediate hypersensitivity mediators from cells, especially mastocytes. In vitro tests show that formoterol is an inhibitor of the release of mediators of tree cells, such as histamine and leukorienes, from the human lung. Formoterol also inhibits the extravagance of histamine-induced plasma albumin in aneti guinea pigs and inhibits the influx of allergen-induced eosinophils into dogs with airway hyper-reactivity. The relevance of these in vitro and animal finds to humans is unknown. Cardiovascular effects of pharmacodynamic asthma In a single-duct cross-study involving 201 patients with persistent asthma, monoduct treatments of 4.5, 9 and 18 mcg of formoterol in combination with 320 mcg of budesonide administered via SYMBICORT were compared with only 320 mcg budesonide. The dose improvements ordered in FEV1 have been demonstrated compared to budesonide. ECG and blood samples for glucose and potassium were obtained after the dose. For SYMBICORT, small average increases in serum glucose and decreased serum potassium (0.44 mmol/L and -0.18 mmol/L respectively at the highest dose) were observed at doses of formotheol, compared to budesonide. In ECG, SYMBICORT produced small dose-related heart rate increases (about 3 bpm at the highest dose) and QTc intervals (3-6 msec) compared to budesonide alone. No subject has had a QT QT QTc value ≥500 msec. In the United States, five 12-week, active-controlled and placebo-controlled studies and a 6-month active controlled study evaluated 2976 patients aged 6 and over with asthma. The systemic pharmacodynamic effects of formoterol (heart rate/pulse, blood pressure, QTc interval, potassium and glucose) were similar in patients treated with SYMBICORT, compared to patients treated with dry inhalation formoterol 4.5 mcg, 2 inhalations twice a day. No patient had a QT or QTc value ≥500 msec during treatment. In three placebo-controlled studies in adolescents and adults with asthma, aged 12 and over, a total of 1232 patients (553 patients in the SYMBICORT group) had continuous electrocardiographic monitoring of 24 hours. Overall, there were no major differences in the occurrence of ventricular or superventricular ectotomy and no evidence of increased risk of clinically significant disrrhythmia in the SYMBICORT group compared to placebo. HPA-Axis effects Overall, no clinically important effects on the HPA axis, measured by urinary cortisol 24 hours, were observed for adult or adolescent patients treated symBICORT at doses up to 640/18 mcg/d compared to budesonide. Chronic obstructive pulmonary disease Cardiovascular effects In two studies of copd lung function, 6 months and 12 months of duration, including 3668 patients with COPD, no clinically important differences in heart rate, blood pressure, potassium and glucose were observed between SYMBICORT, the individual components of SYMBICORT and placebo [see Clinical Studies]. ECGs recorded in multiple clinical visits during treatment in both studies showed no clinically important differences in heart rate, PR range, QRS duration, heart rate, signs of cardiac ischemia, or arrhythmias between SYMBICORT 160/4.5 monoproducts and placebo, all administered as 2 inhalations twice a day. Based on ECG, 6 patients treated with SYMBICORT 160/4.5, 6 patients treated with formoterol 4.5 mcg and 6 patients in the placebo group experienced atrial fibrillation or flutter that was not present at baseline. There were no cases of unsustainable ventricular tachycardia in SYMBICORT 160/4.5, formoterol 4.5 mcg, or placebo groups. In the 12-month study, 520 patients had continuous and assessable monitoring of ECG (Holter) 24 hours before the first dose and after about 1 and 4 months of treatment. No clinically important differences in ventricular or superventricular arrhythmias, ventricular or superventricular ectopic beats, or heart rate were observed among groups treated with SYMBICORT 160/4.5, formoterol or placebo taken as 2 inhalations twice a day. Based on ECG (Holter) monitoring, a patient on SYMBICORT 160/4.5, no on formoterol 4.5 mcg, and three patients in the placebo group experienced atrial fibrillation or flutter that was not present at baseline. Effects of the HPA axis Twenty-four hours of urinary cortisol measurement were collected in a subset of Studies on copco lung function. The data indicated about 30% lower average 24 hours urinary free cortisol values after chronic administration (> 6 months) of SYMBICORT compared to placebo. SYMBICORT appeared to exhibit cortisol suppression comparable to budesonide 160 mcg alone or co-administration of budesonide 160 mcg and formoterol 4.5 mcg. For patients treated with SYMBICORT or placebo for up to 12 months, the percentage of patients who went from normal to low for this measure was generally comparable. Other Budesonide products To confirm that systemic absorption is not a significant factor in the clinical efficacy of inhaled budesonide, a clinical study was performed in asthma patients comparing 400 mcg of budesonide administered via a pressurized dose inhaler with a 1400 mcg tube spacer of oral and placebo budesonide. The study demonstrated the efficacy of inalated but not ingested budesonide orally, despite comparable systemic levels. Thus, the therapeutic effect of conventional doses of inhaled budesonide orally are largely explained by its direct action on the respiratory tract. Inalated budesonide has been shown to decrease airway reactivity to various challenge models, including histamine, metatacholine, sodium metabisulfitis, and adenosine monophosphate in patients with hyperreactive airways. The clinical relevance of these models is not certain. Pretreatment with inhaled budesonide, 1600 mcg per day (800 mcg twice a day) for 2 weeks reduced acute decrease (initial phase reaction) and delayed (late reaction) in FEV1 following an inhaled allergen challenge. The systemic effects of inalated corticosteroids are related to systemic exposure to such drugs. Pharmacological studies have shown that in both adults and children with asthma systemic exposure to budesonide is lower with SYMBICORT than inhaled budesonide administered at the same dose administered via a dry powder inhaler [see CLINICAL PHARMACOLOGY]. Therefore, the systemic effects (HPA axis and growth) of budesonide delivered by SYMBICORT should not be greater than those reported for inhaled budesonide when administered at comparable doses via the dry powder inhaler [see Use in specific populations]. HPA-Axis effects The effects of inhaled budesonide administered via a dry powder inhaler on the HPA axis were studied in 905 adults and 404 paediatric asthma patients. For most patients, the ability to increase cortisol production in response to stress, as assessed by the cosintropin stimulation test (ACTH), remained intact with the treatment of budesonide at recommended doses. For adult patients treated with 100, 200, 400 or 800 mcg twice a day for 12 4%, 2%, 6% and 13%, had an abnormal stimulated response to cortisol (peak cortisol <14.5 mcg/dL evaluated by liquid chromatography after the short-cosyntropin test) compared to 8% of placebo-treated patients. Similar results have been obtained in Patients. In another adult study, doses of 400, 800 and 1600 mcg of inalated budesonide were examined twice a day for 6 weeks; 1600 mcg twice a day (twice the recommended maximum dose) resulted in a 27 per cent reduction in stimulated cortisol (ACTH infusion of 6 hours) while 10mg prednisone resulted in a 35 per cent reduction. In this study, no patients on budesonide at doses of 400 and 800 mcg twice a day met the criterion for an abnormal stimulated-cortisol response (peak cortisol <14.5 mcg/dL evaluated by liquid chromatography) after acth infusion. An open-label and long-term follow-up of 1133 patients for up to 52 weeks confirmed the minimal effect on the HPA (basal cortisol and stimulated-plasma) axis of budesonide when administered at recommended doses. In patients who had previously been oral-steroid-dependent, the use of budesonide in recommended doses was associated with a higher stimulated-cortisol response than the baseline after 1 year of therapy. Other Formoterol products While the pharmacodynamic effect is through stimulation of beta-adrenergic receptors, excessive activation of these receptors commonly leads to skeletal muscle tremor and cramps, insomnia, tachycardia, decreases in potassium plasma, and increases plasma glucose. Inhaled formoterol, like other beta2-adrenergic agonist drugs, can produce dose-related cardiovascular effects and on the effects of potassium of blood glucose and/or serum [see WARNINGS AND PRECAUTIONS]. For SYMBICORT, these effects are detailed in the section Clinical Pharmacology, Pharmacodynamics, SYMBICORT (12.2). The use of LABA drugs can cause tolerance to bronchoprotective and bronchodilative effects. Bronchial rebound hyperresponsance was not observed after the cessation of long-acting chronic beta-agonist therapy. Pharmacokinetics SYMBICORT Budesonide absorption Healthy budesonide orally inhaled budesonide subjects is quickly absorbed into the lungs and peak concentration is typically reached within 20 minutes. After oral administration of peak plasma concentration of budesonide was reached in about 1 to 2 hours and absolute systemic availability was 6%-13% due to extensive first-step metabolism. In contrast, most of the budesonide delivered to the lungs has been systemically absorbed. In healthy subjects, 34% of the measured dose was deposited in the lung (as evaluated by the plasma concentration method and using a dry powder inhaler containing budesonide) with an absolute systemic availability of 39% of the measured dose. After administration of SYMBICORT 160/4.5, two or four inhalations twice a day for 5 days in healthy subjects, the plasma concentration of budesonide is generally increased in proportion to the dose. accumulation for the group that received 2 inhalations twice a day was 1.32 per budesonide. Asthma patients In a single dose study, doses higher than those recommended for SYMBICORT (12 symbicort 160/4.5 inhalations) were administered to patients with moderate asthma. Peak budesonide plasma concentration of 4.5 nmol/L nmol/L 20 minutes after dosing. This study showed that symbicort's total systemic exposure to budesonide was about 30% lower than budesonide inhaled via a dry powder inhaler (PPE) at the same dose administered. After the administration of SYMBICORT, the Ethiopic of the budesonide component was 4.7 hours. In a repeated dose study, the highest recommended dose of SYMBICORT (160/4.5, two inhalations twice a day) was given to patients with moderate asthma and healthy subjects for 1 week. The peak budesonide plasma concentration of 1.2 nmol/L occurred at 21 minutes in asthmatic patients. The peak plasma budesonide concentration was 27% lower in asthmatic patients than in healthy subjects. However, total systemic exposure of budesonide was comparable to that of asthmatic patients. The maximum concentrations of budesonide-state plasma administered by IPR in adults with asthma averaged 0.6 and 1.6 nmol/L at doses of 180 mcg and 360 mcg twice a day, respectively. In asthmatic patients, budesonide showed a linear increase in AUC and Cmax with increasing dose after the single and repeated dosage of inhaled budesonide. Patients with COPD In a single dose study, 12 inhalations of SYMBICORT 80/4.5 (total dose 960/54 mcg) were administered to patients with COPD. The average peak plasma concentration of budesonide of 3.3 nmol/L occurred 30 minutes after dosing. The systemic exposure of Budesonide was comparable between SYMBICORT pMDI and the co-administration of budesonide via a measured dose inhaler and formoterol via a dry powder inhaler (budesonide 960 mcg and formoterol 54 mcg). In the same study, an open-label group of moderate asthma patients also received the same highest dose of SYMBICORT. For budesonide, COPD patients exhibited 12% higher AUC and 10% lower Cmax than asthmatic patients. In the clinical study of 6-month pivotal lung function, stable-state pharmacological data of budesonide were obtained in a subset of COPD patients with treatment arms of SYMBICORT pMDI 160/4.5, SYMBICORT pMDI 80/4.5, budesonide 160 mcg, budesonide 160 mcg and formoterol 4.5 mcg administered together, all administered as 2 in twice a day. Systemic budesonide exposure (AUC and Cmax) increased proportionally with doses from 80 mcg to 160 mcg and was generally similar among the 3 treatment groups receiving the same dose of budesonide (SYMBICORT pMDI 160/4.5, budesonide 160 mcg, budesonide 160 mcg and formoterol 4.5 mcg administered together). Formoterol Inhaled formoterol is rapidly absorbed; peak plasma concentrations are typically reached at the first plasma sampling time, within 5-10 minutes after dosing. As with many pharmacological for oral inhalation, it is likely that most of the delivered inhaled formoterol is ingested and then absorbed by the gastrointestinal tract. Healthy subjects After administration of SYMBICORT (160/4.5, two or four inhalations twice a day) for 5 days in healthy subjects, plasma concentration of formoterol generally generally in proportion to the dose. The accumulation index for the group that received 2 inhalations twice a day was 1.77 for formoterol. Asthma patients In a single dose study, doses higher than those recommended for SYMBICORT (12 symbicort 160/4.5 inhalations) were administered to patients with moderate asthma. The peak plasma concentration for formoterol of 136 pmol occurred 10 minutes after dosing. About 8% of the administered dose of formoterol was recovered in the urine as an unchanged drug. In a repeated dose study, the highest recommended dose of SYMBICORT (160/4.5, two inhalations twice a day) was given to patients with moderate asthma and healthy subjects for 1 week. The maximum plasma

formoterol concentration of 28 pmol/L occurred at 10 minutes in asthmatic patients. The maximum plasma concentration for formoterol was about 42% lower in asthmatic patients than in healthy subjects. However, the total systemic exposure of formoterol was comparable to that of asthmatic patients. Copd patients Following administration of a single dose of 12 symbicort 80/4.5 inhalations, the average permoterol plasma concentration of 167 pmol/L was quickly reached 15 minutes after the dosage. Exposure to the formotelo was slightly higher (16-18%) by SYMBICORT pMDI with respect to the co-administration of budesonide by measured dose inhaler and formoterol via a dry powder inhaler (total dose of budesonide 960 mcg and formoterol 54 mcg). In the same study, a group of patients with moderate asthma received the same dose of SYMBICORT. COPD patients exhibited 12-15% more AUC and Cmax for formoterol than asthmatic patients. In the clinical study of 6-month pivotal lung function, the constant state pharmacokinetic data of formoterol were obtained in a subset of COPD patients with treatment arms of SYMBICORT pMDI 160/4.5, SYMBICORT pMDI 80/4.5, formoterol 4.5 mcg, budesonide 160 mcg and formoterol 4.5 mcg administered together, all administered as 2 inhalations twice a day. Systemic exposure of formoterol, as evidenced by the AUC, was about 30% and 16% higher than the formoterol-only treatment arm and the co-administration of the individual components of the budesonide and formoterol treatment arm, respectively. Budesonide distribution The distribution volume of the budesonide was about 3 L/kg. It was 85%-90% protein-related. The protein bond was constant with respect to the concentration range (1-100 nmol/L) reached with, and exceeding, the recommended inhaled doses. Budesonide has shown little or no link to corticosteroid binding globulin. Budesonide quickly balanced with red blood cells independently of the with a blood plasma ratio of about 0.8. Formoterol Beyond the concentration range of 10-500 nmol/L, the plasma protein association for formoterol RR and SS enantiors was 46% and 58% respectively. The concentrations of formoterol used to assess the binding of the plasma protein were higher than those obtained in plasma after inhalation of a single dose of 54 mcg. Mcg. Budesonide In vitro studies with human liver homogeneous have shown that budesonide has been rapidly and widely metabolized. Two major metabolites formed by cytochrome P450 (CYP) isoenzyme 3A4 (CYP3A4) have been isolated and identified as 16 -hydroxyprednisolone and 6ÃŸ-hydroxide hydroxide. The corticosteroid activity of each of these two metabolites was less than 1% of that of the parent compound. No qualitative differences were found between in vitro and in vivo metabolic models. Negligible metabolic inactivation has been observed in human lung and serum preparations. Formoterol The primary metabolism of formoterol is by direct glucuronidation and O-demethylation followed by conjugation to inactive metabolites. Secondary metabolic pathways include deformilation and sulfate conjugation. CYP2D6 and CYP2C have been identified as responsible for the Odemetilation. Elimination Budesonide Budesonide was excreted in the urine and feces in the form of metabolites. About 60% of an endovenous dose with radio labeling was recovered in the urine. No unchanged budesonide was detected in the urine. The 22R form of budesonide was preferentially erased from the liver with systemic customs clearance of 1.4 L/min versus 1.0 L/min for the 22S form. The terminal hemita, 2 to 3 hours, was the same for both epimers and was dose independent. Formoterol Formoterol excretion has been studied in four healthy subjects following simultaneous administration of formoterol radiolabeled through oral and IV routes. In this study, 62% of radiolabeled formoterol was excreted in the urine, while 24% was eliminated in the faeces. Special populations Geriatrics Symbicort pharmacokinetics in geriatric patients has not been specifically studied. Paediatric plasma concentrations of budesonide were measured after four inhalations of SYMBICORT 160/4.5 were administered in a single-dose study in paediatric asthma patients, from 6 to less than 12 years of age. Peak budesonide concentrations of 1.4 nmol/L occurred 20 minutes after the dose. This study also showed that symbicort's total systemic exposure to budesonide was about 30% lower than budesonide inhaled via a dry powder inhaler that was also evaluated at the same dose administered. Dose-normalized Cmax and budesonide AUC0-inf as a result of single dose inhalation in children ages 6 to 12 were numerically lower than those observed in adults. Following 2 inhalations of SYMBICORT 160/4.5 twice daily treatment, formoterol Cmax and stable state AUC0-6 in 6 children under 12 years of age were comparable to that observed in adults. No gender/race specific studies have been conducted to examine the effects of gender and race on SYMBICORT pharmacokinetics. PK of the data population SYMBICORT indicates that gender does not affect the pharmacokinetics of the budesonide and formotelo. No conclusions can be drawn on the effect on the due to the low number of non-Caucasians rated for PK. Nursing mothers The arrangement of budesonide when administered by inhalation from a dry powder inhaler at doses of 200 or 400 mcg twice a day for at least 3 months has been studied in eight women who breastfeed with asthma 1 to 6 months after calving. Systemic exposure to budesonide in these women appears to be comparable to that of non-pregnant women with asthma from other studies. Breast milk obtained within eight hours post-dose revealed that the maximum concentration of budesonide for the total daily doses of 400 and 800 mcg was 0.39 and 0.78 nmol/L respectively, and occurred within 45 minutes of the dosage. The estimated oral daily dose of budesonide from breast milk to the newborn is about 0.007 and 0.014 mcg/kg/day for the two dose regimens used in this study, which represents about 0.3% to 1% of the dose inalated by the mother. Budesonide levels in plasma samples obtained from five infants about 90 minutes after lactation (and about 140 minutes after administering drugs to the mother) were below quantifiable levels (<0.02 nmol/L in four infants and <0.04 nmol/L in a newborn) [see Use in specific populations]. Renal or liver failure There is no data regarding the specific use of SYMBICORT in patients with liver or kidney impairment. Reduction of liver function can affect the elimination of corticosteroids. Budesonide pharmacokinetics was affected by impaired liver function as evidenced by systemic availability doubled after oral ingestion. Endovenous budesonide pharmacokinetics was, however, similar in cirrhosis patients and healthy subjects. Specific data with formoterol is not available, but because formoterol is mainly eliminated by liver metabolism, an increase in exposure can be expected in patients with severe liver deficit. Drug-drug interactions A single-dose crossover study was conducted to compare the pharmacokinetics of eight inhalations of the following: budesonide, formoterol, and budesonide plus formoterol administered at the same time. The results of the study indicated that there was no evidence of a pharmacokinetic interaction between the two components of SYMBICORT. Cytochrome P450 Enzymes Ketoconazole Ketoconazole inhibitors, a strong cytochrome P450 (CYP) inhibitor isoenzyme 3A4 (CYP3A4), the main metabolic enzyme for corticosteroids, increased levels of orally ingested budesonide plasma. Cimetidine At the recommended doses, cimetidine, a non-specific inhibitor of CYP enzymes, had a mild but clinically insignificant effect on the pharmacokinetics of oral budesonide. Specific drug-drug interaction studies with formoterol have not been performed. Animal toxicology and/or preclinical pharmacological studies in animals to be (minipigs, rodents and dogs) have demonstrated the onset of cardiac arrhythmias and sudden death (with histological evidence of myocardial necrosis) when beta-agonists and methylxanthines methylxanthines are administered The clinical significance of these results is unknown. Clinical studies Asthma patients with asthma 12 years of age and the elderly In two clinical trials comparing SYMBICORT with individual components, improvements in most efficacy endpoints were greater with SYMBICORT than with the use of budesonide or formoterol alone. In addition, a clinical study showed similar results between SYMBICORT and the simultaneous use of budesonide and formoterol at corresponding doses from separate inhalers. The safety and efficacy of SYMBICORT has been demonstrated in two randomized, double-blind, placebo-controlled clinical trials in the United States involving 1076 patients aged 12 and over. Correct symbicort dosages of 160/9 mcg and 320/9 mcg twice a day (each dose administered as 2 inhalations of 80/4.5 and 160/4.5 mcg strengths, respectively) were compared with the monocomponents (budesonide and formoterol) and placebo to provide information on the appropriate dosage to cover a range of asthmatic severity. Study 1: Clinical Trial with SYMBICORT 160/4.5 This 12-week study evaluated 596 patients aged 12 and over comparing SYMBICORT 160/4.5, the free combination of budesonide 160 mcg plus formoterol 4.5 mcg in separate inhalers, budesonide 160 mcg, formoterol 4.5 mcg, and placebo; each administered as 2 inhalations twice a day. The study included a 2-week run-in period with 80 mcg budesonide, 2 inhalations twice a day. Most patients had moderate to severe asthma and used moderate to high doses of inalated corticosteroids before entering the study. Randomization was stratified by previous treatment with inhaled corticosteroid (71.6% on moderate dose inhaled corticosteroids and 28.4% on high-dose inhaled corticosteroids). The expected average fev1 baseline was 68.1% and was similar among treatment groups. The endpoints of co-primary efficacy were average post-dose FEV1 of 12 hours per week 2 and FEV1 pre-dose average during the course of the study. The study also required the withdrawal of patients who met a default asthma worsening criterion. The default criteria for worsening asthma were a clinically significant decrease in FEV1 or PEF, an increase in the use of rescue albutyrol, night awakening due to asthma, emergency intervention or hospitalization due to asthma, or the requirement for asthma medications not permitted by protocol. For the criterion of night awakening due to asthma, patients were allowed to remain in the study at the discretion of the investigator if none of the other criteria for worsening asthma were met. The percentage of patients retiring due to or meeting predefined criteria for asthma degradation is shown in Table 4. TABLE 4 : The number and of patients retiring due to or meeting predefined criteria for asthma worsening (Study 1) SYMBICORT 160/4.5 n - 124 Budesonide 160 mcg plus Formoterol 4.5 mcg n Budesonide 160 mcg n . 109 Formoterol 4.5 mcg n - 123 Placebo n - 125 Patients withdrawn due to a default asthma event1 13 (10.5) 13 (11.3) 22 22 44 (35,8) 62 (49,6) Pazienti con un evento di asma predefinito1,2 37 (29,8) 24 (20,9) 48 (44,0) 68 (55,3) 84 (67,2) Diminuzione in FEV1 4 (4(44,0) 68 (55,3) 84 (67,2) Diminuzione in FEV1 4 (4(44,0) 68 (55,3) 84 (67,2) Diminuzione in FEV1 4 (4 (44,0) 3.2) 8 (7.0) 7 (6.4) 15 (12.2) 14 (11.2) Uso dei farmaci da soccorso 2 (1.6) 0 3 (2.8) 3 (2.4) 7 (5.6) Diminuzione in AM PEF 2 (1.6) 5 (4.3) 5 (4.6) 17 (13.8) 15 (12.0) Risvegli notturni3 24 (19.4) 11 (9.6) 29 (26.6) 32 (26.6) 49 (39,2) Esacerbazione clinica 7 (5.6) 6 (5.2) 5 (4.6) 17 (13,8) 16 (12,8) 1Questi criteri sono stati valutati su base giornaliera indipendentemente dalla tempistica della visita in clinica , with the exception of FEV1, which was evaluated at each clinical visit. 2 Individuali criteria are displayed for patients who meet any default asthma event, regardless of withdrawal status. 3For the criterion of night awakening due to asthma, patients were allowed to remain in the study at the discretion of the investigator if none of the other criteria were met. The average percentage change from the baseline in FEV1 measured immediately before the dosage (pre-dose) for 12 weeks is shown in Figure 1. Since this study used predefined withdrawal criteria for asthma worsening, which caused a differential withdrawal rate in treatment groups, pre-dose FEV1 results are also provided on the last available study visit (end of treatment, EOT). Patients who received SYMBICORT 160/4.5 had significant improvements compared to the baseline in the pre-dose FEV1 at the end of treatment (0.19 L, 9.4%), compared to budesonide 160 mcg (0.10 L, 4.9%), formoterol 4.5 mcg (-0.12 L, -4.8%) and placebo (-0.17 L, -6.9%). Figure 1 : Change in the average percentage compared to the forecast in pre-dose FEV1 over 12 weeks (Study 1) The effect of SYMBICORT 160/4.5 two inhalations twice a day on selected secondary efficacy variables, including morning and evening PEF, albutyrol relief use and asthma symptoms over 24 hours on a 0-3 scale is shown in Table 5. TABLE 5 : Average values for selected secondary efficacy variables (Study 1) SYMBICORT efficacy variable 160/4.5 (n1-124) Budesonide 160 mcg plus Formoterol 4.5 mcg (n1-115) Budesonide 160 mcg (n1-109) Formoterol 4.5 mcg (n1-115) LCY (L/min) Base 341 338 339 355 339 355 Change from baseline 35 28 9 -9 -18 PM PEF (L/min) Baseline 351 348 357 354 3 69 Change from baseline 34 26 7 -7 -18 Albuterol rescue use Baseline 2.1 2.3 2.7 .5 2.4 Variation from Baseline -1.0 -1.5 -0.8 -0.3 0.8 Average symptom/day score (0.8 0-3 scale) Expected 0.99 1.03 1.04 1.04 1.08 Baseline variation -0.28 -0.32 -0.14 -0.05 0.10 1 The number of patients (n) varies slightly due to the number of patients for whom available data for each variable. The results displayed are based on the latest available data for each variable. The subjective impact of asthma on patients' quality of life was assessed through the use of the Standardised Asthma Quality of Life Questionnaire (AQLQ(S)) (based on a 7-point scale where 1 - maximum damage and 7 - no harm). Patients who received SYMBICORT 160/4.5 had a clinically significant significant improvement quality of life, as defined by an average difference between treatment groups of >0.5 points in variation from baseline in the overall AQLQ score (difference in AQLQ score of 0.70 [95% CI 0.47, 0.93], compared to placebo). Study 2: Clinical trial with SYMBICORT 80/4.5 This 12-week study was similar in design to study 1 and included 480 patients aged 12 and over. This study compared SYMBICORT 80/4.5, budesonide 80 mcg, formoterol 4.5 mcg, and placebo; each administered as 2 inhalations twice a day. The study included a 2-week placebo run period. Most patients had mild to moderate asthma and used low to moderate doses of inalated corticosteroids before entering the study. The expected average fev1 percentage at baseline was 71.3% and was similar among treatment groups. The efficacy variables and endpoints were identical to those in study 1. The percentage of patients retiring due to or meeting predefined criteria for asthma deterioration is shown in Table 6. The evaluation method and criteria used were identical to that of study 1. Tabella 6 : Il numero e la percentuale di pazienti che si ritirano a causa o soddisfano criteri predefiniti per il peggioramento dell'asma (Studio 2) SYMBICORT 80/4.5 (n.123) Budesonide 80 mcg (n.121) Formoterol 4.5 mcg (n.114) Placebo (n.122) Pazienti ritirati a causa di un evento di asma predefinito1 99 (79 .3) 8 (6.6) 21 (18.4) 40 (32.8) Pazienti con un evento di asma predefinito1,2 23 (18,7) 26 (21,5) 48 (42,1) 69 (56,6) Diminuzione in FEV1 3 (2,4) 3 (3) 3 (3) 3 (3) 2.5) 11 (9.6) 9 (7.4) Uso di farmaci di salvataggio 1 (0,8) 3 (2,5) 1 (0,9) 3 (2,5) Diminuzione in AM 3 (2.4) 1 (0,8) 8 (7,0) 14 (11,5) PEF risveglio3 17 (13.8) 20 (16.5) 31 (27.2) 52 (42.6) Esacerbazione clinica 1 (0.8) 3 (2.5) 5 (4.4) 20 (16.4) 1 Questi criteri sono stati valutati su base giornaliera indipendentemente dalla tempistica della visita clinica visitata , with the exception of FEV1, which was evaluated at each clinical visit. 2 Individual criteria are displayed for patients who meet any default asthma event, regardless of withdrawal status. 3 For the criterion of night awakening due to asthma, patients were allowed to remain in the study at the discretion of the investigator if none of the other criteria were met. The average percentage change from the 12-week pre-dose FEV1 forecast is shown in Figure 2. Figure 2 : Change in the average percentage compared to forecast in the pre-dose FEV1 over 12 weeks (Study 2) The efficacy results for other secondary endpoints, including quality of life, were similar to those observed in study 1. Onset and duration of action and progression of improvement in asthma control The onset of action and improvement in asthma control were evaluated in the two key clinical trials. The median time for the onset of clinically significant bronchosulation (>15% improvement in FEV1) was seen within 15 minutes. The greatest improvement in FEV1 occurred within 3 hours, and clinically significant improvement was maintained over the course of 12 hours. Figures 3 and 4 show the percentage change from the baseline in post-dose FEV1 over 12 hours randomization and the last day of treatment for study 1. The reduction of asthma symptoms and in the rescue use of albutyrol, as well as improvement in morning and evening PEF, occurred within 1 day of the first dose of SYMBICORT; improvement of these variables was maintained during the 12 weeks of therapy. After the initial dose of SYMBICORT, FEV1 improved significantly during the first 2 weeks of treatment, continued to show improvements in week 6 evaluation, and was maintained until week 12 for both studies. No decrease in the 12-hour broncholyptic effect was observed with SYMBICORT 80/4.5 or SYMBICORT 160/4.5, as evaluated by FEV1, after 12 weeks of therapy or on the last available visit. The FEV1 data from Study 1 evaluating symBICORT 160/4.5 are shown in Figures 3 and 4. Figure 3 : Change in the average percentage compared to the forecast in FEV1 on the day of randomisation (Study 1) Figure 4 : Change in the average percentage compared to the forecast in FEV1 at the end of treatment (study 1) Patients with asthma 6 under 12 years of age The clinical programme to support the efficacy of SYMBICORT 80/4.5 in children from 6 to less than 12 years of age including the following: 1) a confirmatory study of the dose of budesonide, 2) a research study of the dose of formoterol, and 3) a study of the efficacy and safety of the combined product SYMBICORT. The selection of 80 mcg budesonide is supported by a 6-week, randomized, double-blind, placebo-controlled study in 304 pediatric patients (152 budesonide, 152 placebos) 6 under 12 years of age with asthma. The results showed that budesonide 80 mcg (2 inhalations twice a day) provided a statistically significantly higher improvement than placebo for the primary endpoint of the change from baseline to average treatment period in pre-dose morning PEF and key secondary endpoint of change in pre-dose morning FEV1. The selection of the formoterol dose is supported by a single randomized, placebo-controlled, active controlled dose (Foradil Aerolizer 12 mcg), a 5-way cross-study in which doses of 2.25, 4.5 and 9 mcg of formoterol were administered in combination with budesonide in 54 pediatric patients from 6 to less than 12 years of age with asthma. The results showed a dose response of formoterol versus placebo for the average 12-hour post-dose FEV1 primary endpoint, and the 9 mcg group showed numerically similar results compared to active control. The confirmatory efficacy study was a 12-week, randomized, double-blind multicenter study in which SYMBICORT 80/4.5 was compared with 80 mcg pMDI budesonide, each administered as 2 inhalations twice a day, in 184 pediatric patients ages 6 to under 12 years of age with documented clinical diagnosis of asthma. At the entrance to the study, children had a requirement for inhaled corticosteroid therapy of daily mid-range or a fixed combination of inhaled corticosteroid and LABA therapy, and showed symptoms despite treatment with a low-dose inhaled corticosteroid during a 2-4 week run period. The primary primary variable was variable from the baseline to week 12 in FEV1 of 1 hour after the dose measured in the clinic. In patients receiving SYMBICORT 80/4.5, there was a statistically significant change from budesonide in 1 hour post-dose FEV1 which improved by 0.28 L from baseline to week 12, compared to 0.17 L for those receiving 80 mcg budesonide (average difference 0.12 L; 95% CI: 0.03, 0.20) (see Figure 5). Figure 5: Change from baseline in post-dose FEV1 measured in 1 hour over 12 weeks (Efficacy and safety study in patients 6 to under 12 years of age). Similarly, an improvement in the change from baseline to week 12 for the PEF post-dose clinic of 1 hour was observed (average difference of 25.5 L/min; 95% CI: 10.9, 40.0). The bronchodilator effects were evident from the first evaluation to 15 minutes on day 1 and were maintained at week 12. The estimated average difference between SYMBICORT 80/4.5 and budesonide compared to the change from baseline to week 12 in 15 minutes after the FEV1 clinical dose was 0.10 L (95% CI: 0.02, 0.18). No difference between SYMBICORT and budesonide was noted in night awakenings, use of rescue albutyrol or paediatric asthma quality of life (PAQLQ) questionnaire scores. The percentage of patients with at least 0.5 baseline improvement points in Week 12 in PAQLQ was 42% on SYMBICORT 80/4.5 and 46% on budesonide 80 mcg. Post-market safety and efficacy study A randomized, double-blind, parallel-group study compared SYMBICORT with budesonide, each administered as 2 inhalations twice a day for 26 weeks (NCT01444430). The primary safety objective was to assess whether the addition of formoterol to budesonide therapy (SYMBICORT) was not lower than budesonide in terms of the risk of serious asthma-related events (asthma-related hospitalization, endotracheal intubation, and death). The study is designed to exclude a predefined risk margin for severe asthma-related events of 2.0. A blind judgment committee determined whether the events were related to asthma. This study enlisted patients over the age of 12, had a clinical diagnosis of asthma for at least 1 year, and had at least 1 asthma exacerbation requiring treatment with systemic corticosteroids or asthma-related hospitalization in the previous year. Patients were layered at one of two dose levels of SYMBICORT or budesonide based on the evaluation of asthma control and ongoing asthma therapy. Patients with a history of potentially raised asthma have been excluded. The study included 11,693 patients [5846 who received SYMBICORT (80/4.5 or 160/4.5) and 5847 receiving budesonide (80 or 160 mcg)], whose average age was 44 years old, and of which 66% were female and 69% were Caucasian. SYMBICORT was no less than budesonide in terms of time for the first serious asthma-related events based on the pre-specified risk margin, with an estimated risk ratio of 1.07 [95% CI: 0.70, 1.65] (Table 7). TABLE 7 : Serious asthma-related events (post-marketing study on safety and efficacy) SYMBICORT (N1 No 5846) 5846) (%) Budesonide (N1 #5847) n2 (%) SYMBICORT vs Budesonide Hazard ratio (95% CI)3 Severe asthma-related event4 43 (0.7) 40 (0.7) 1.07 (0.70, 1.65) Asthma-related death 2 (<0.1) 0 Endotracheal intubation related to asthma 1 (<0.1) 0 Asthma-related hospitalization 42 (0.7) 40 (0.7) 1N - total number of patients 2n - number of patients with event 3The risk ratio for time at the first event was based on an unstratified Cox proportional risk model with treatment covariates (SYMBICORT vs. budesonide) and the dose level of inhaled corticosteroid (160 mcg versus 80 mcg), as randomized. If the resulting higher CI estimate for relative risk was < 2.0, then the non-inferiority was concluded. 4Societement related to asthma, endotracheal intubation or death occurred within 6 months of the first use of the study drug or 7 days after the last date of the study drug, depending on the next date. Patients may have one or more events, but only the first event has been counted for analysis. A single independent, blinded and blind judgment committee determined whether the events were related to asthma. The primary endpoint of efficacy was asthma exacerbation, defined as a deterioration in asthma that led to the use of systemic corticosteroids for at least 3 days, or a hospitalization, or a visit to the emergency room that required systemic corticosteroids. The estimated risk ratio for time and the first asthma exacerbation rate for SYMBICORT compared to budesonide was 0.84 [95% CI: 0.75, 0.94]. This result was mainly driven by a reduction in the use of systemic corticosteroids. Chronic obstructive pulmonary function Pulmonary function The efficacy of SYMBICORT 80/4.5 and SYMBICORT 160/4.5 in the treatment of maintaining airflow obstruction in COPD patients has been evaluated in two randomised patients, double-blind, placebo-controlled multinational studies conducted over 6 months (Study 1) and 12 months (Study 2), out of a total of 3668 patients (2416 males and 1252 females). Most patients (93%) were Caucasian. All patients had to be at least 40 years of age, with FEV1 less than or equal to the expected 50%, a clinical diagnosis of COPD with symptoms for at least 2 years, and a smoking history of at least 10 years, before entering the study. The average basal FEV1 prebronchodilator of patients enrolled in the study was expected to be 34%. 48% of enlisted patients were on inalated corticosteroids and 52.7% of patients were in short-acting anticholinegic bronchodilatars during run-in. On randomization, inalated corticosteroids were discontinued, and ipratropium bromide was allowed at a stable dose for those patients previously treated with short-acting anti-ndic bronchodilitis. Co-primary efficacy variables in studies were the change from baseline to pre-dose average and 1 hour post-dose FEV1 in the treatment period. The results of both studies 1 and 2 are described below. Study 1 A 6-month placebo-controlled study occurred in 1704 COPD patients (% mean % Baseline FEV1 from 33.5% -34.7%) to demonstrate the efficacy and safety of SYMBICORT in the treatment of airflow obstruction in COPD. Patients were randomised in one of the following treatment groups: SYMBICORT 160/4.5 (n.277), SYMBICORT 80/4.5 (n.281), budesonide 160 mcg - formoterol 4.5 mcg (n.287), budesonide 160 mcg (n.275), formoterol 4.5 mcg (n.284) or placebo (n.300). Patients receiving SYMBICORT 160/4.5, two inhalations twice a day, had significantly greater average improvements than baseline in the fev1 pre-dose average over the treatment period [0.08 L, 10.7%] compared to formoterol 4.5 mcg [0.04 L, 6.9%] and placebo [0.01 L, 2.2%] (see Figure 6). Patients who received SYMBICORT 80/4.5, two inhalations twice a day, did not have a significantly higher improvement than baseline in the mediated pre-dose FEV1 over the treatment period compared to formoterol 4.5 mcg. Figure 6 : Change in average percentage compared to forecast in 6-month pre-dose FEV1 (Study 1) Patients receiving SYMBICORT 160/4.5, two inhalations twice a day, had significantly greater average improvements than the baseline in 1 hour after the average FEV1 dose in the treatment period [0.20 L, 22.6%], compared to budesonide 160 mcg [0.03 L, 4.9%] and placebo [0.03 L, 4.1%] (see Figure 7). Figure 7 : Average percentage change from 1 hour post-dose FEV1 forecast over 6 months (Study 1) Study 2 This was a 12-month placebo-controlled study of COPD patients in 1964 (baseline FEV1 expected average of 33.7% -35.5%) to demonstrate the efficacy and safety of SYMBICORT in the treatment of airflow obstruction in COPD. Patients were randomized in one of the following treatment groups: SYMBICORT 160/4.5 (n.494), SYMBICORT 80/4.5 (n.494), formoterol 4.5 mcg (n.495) or placebo (n.481). Patients who received SYMBICORT 160/4.5, two inhalations twice a day, had significantly greater improvements than baseline in the fev1 pre-dose average over the treatment period [0.10 L, 10.8%] compared to formoterol 4.5 mcg [0.06 L, 7.2%] and placebo [0.01 L, 2.8%]. Patients who received SYMBICORT 80/4.5, two inhalations twice a day, had no significantly higher improvement than baseline in fev1 pre-dose average over the treatment period compared to formoterol. Patients who received SYMBICORT 160/4.5, two inhalations twice a day, also had significantly greater average improvements than baseline in 1 hour after fev1 dose on average over the treatment period [0.21 L, 24.0%] compared to placebo [0.02 L, 5.2%]. Fev1 serial measurements of more than 12 hours were obtained in a subset of patients in study 1 (n.99) and study 2 (n.121). The median time for the onset of defined as an FEV1 increase of 15% or higher than baseline, occurred 5 minutes after the dose. The maximum improvement (calculated as an average change from the forecast at each point of time) in FEV1 occurred about 2 hours after the dose. In both studies 1 and 2, improvements in morning and evening secondary endpoints the heretical flow and reduction of the use of rescue drugs supported the effectiveness of SYMBICORT 160/4.5. Exacerbations Studies 3 and 4 were designed primarily to assess the effect of SYMBICORT 160/4.5 on COPD exacerbations. Study 3 This was a 6-month active control study conducted to assess the effect of SYMBICORT 160/4.5 compared to formoterol 4.5 mcg, each administered as 2 inhalations twice a day, on the rate of moderate and severe exacerbations of COPD. COPD exacerbations have been defined as worsening of 2 or more major symptoms (dyspnea, volume of sputum, color/purulence of sputum) or worsening of any main symptom along with at least 1 of the minor symptoms: sore throat, cold (nasal discharge and/or nasal congestion), fever without other causes, increased cough or increased breathing for at least 2 consecutive days. COPD exacerbations were considered to be of moderate severity if treatment of symptoms with systemic corticosteroids (≥3 days) and/or antibiotics was necessary, and were considered severe if hospitalization was required. The randomized study 1219 subjects to SYMBICORT 160/4.5 (606) and formoterol 4.5 mcg (613) of which 57% were males and 92% were Caucasian. They had an average age of 64 and a median smoking history of 39 years, with 46% identified as current smokers. At run-in, the average % expected post-bronchodilator FEV1 normal was 48.7% (interval: 16.0% to 78.1%), and patients had a history of at least 1 COPD exacerbation in the previous year treated with systemic corticosteroids and/or hospitalization. All subjects were treated with SYMBICORT 160/4.5, two inhalations twice a day during a 4-week period before being assigned to the trial treatment. Study 4 This was a 12-month active control study, which included 811 subjects treated with SYMBICORT 160/4.5 or formoterol 4.5 mcg, each administered as 2 inhalations twice a day. The study was conducted to assess the reduction of COPD exacerbation in COPD patients. COPD exacerbations have been defined as worsening COPD which required a course of oral steroids for treatment and/or hospitalization. This randomized study 407 subjects to SYMBICORT 160/4.5 and 404 to formoterol 4.5 mcg of which 61% were males and 83% were Caucasian. They had an average age of 63 and a median smoking history of 45 years, with 36% identified as current smokers. At run-in, the expected normal FEV1 average post-bronchodilator was 37.8% (range: 11.75% to 76.50%), and a history of at least 1 COPD exacerbation in the previous year treated with systemic corticosteroids and/or antibiotics. In study 3, subjects treated with SYMBICORT 160/4.5, two inhalations twice a day had a significantly higher annual rate moderate/severe copco exacerbations compared to formoterol 4.5 mcg with a reduction of 26% (95% CI: 9%, 39%). In study 4, a significantly lower annual rate of exacerbations was also observed in subjects treated with SYMBICORT 160/4.5 compared to formoterol 4.5 mcg with a reduction of 35% (95% CI: CI: 47%) (Table 8). TABLE 8 : Treatment of exacerbations of chronic obstructive pulmonary disease n Symbicort Reference Annual Rate 160/4.5 vs. Formoterol 4.5 mcg Estimate 95% CI Study 3 SYMBICORT 160/4.5 606 0.94 0.74 0.61, 0.91 Formoterol 4.5 mcg 613 1.27 Studio 4 SYMBICORT 160/4.5 404 0.68 0.65 0.53, 0.80 Formoterol 4.5 mcg 403 1.05 n – Number of patients included in the efficacy analysis set. Health-related quality of life was measured using St George's Respiratory Questionnaire (SGRQ) in both clinical studies on COPD exacerbation. In Study 3, 6-month SGRQ response rates (defined as an improvement in the score of 4 or more as a threshold) were 40% and 33% for SYMBICORT 160/4.5 and formoterol 4.5 mcg, respectively, with a quota ratio of 1.5 (95% CI: 1.0, 2.0) for SYMBICORT 160/4.5 vs. formoterol 4.5 mcg. In study 4, 12-month response rates were 50% and 49% respectively for SYMBICORT 160/4.5 and formoterol 4.5 mcg, with a probability ratio of 1.0 (95% CI: 0.8, 1.4) for SYMBICORT 160/4.5 vs. formoterol 4.5 mcg. Mcg.