SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

AIRTIDE 500mcg/50 mcg Capsules for Inhalation

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:
Within each inhalation capsule:

salmeterol xinafoate*	72.5 mcg
fluticasone propionate	500 mcg

*equal to 50 mcg salmeterol

Excipients:

Lactose monohydrate	12,3275 mg (cow milk is sourced)

See section 6.1 for excipients.

3. PHARMACEUTICAL FORM

Capsules for inhalation
White or whitish powder in a colorless capsule

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

It is used for the correction and control of asthma symptoms. It is given in the treatment of asthma from the 3rd step. Reduces symptoms and attack frequency in moderate to severe COPD cases.

4.2 Posology and method of administration

Posology/administration frequency and time:
AIRTIDE is for inhalation use only.

Patients should be made aware that AIRTIDE must be used regulary for optimum benefit, even when asymptomatic.

Patients should be regularly reassessed by a doctor, so that the strength of AIRTIDE they are receiving remains optimal and is only changed on medical advice.
Alternatively, in patients requiring long-acting beta$_2$-agonists, AIRTIDE may be titrated to once daily if, in the opinion of the prescribing physician, it is considered sufficient to achieve disease control. If the patient has a history of nocturnal symptoms and is dosing once a day, the dose should be given at night; If the patient has a history of symptoms that usually occur during the daytime, the dose should be given in the morning.

Asthma
The dose should be titrated to the lowest dose at which effective control of symptoms is maintained. Where the control of symptoms is maintained with the lowest strength of the AIRTIDE given twice daily then the next step could include a test of once a day.

Patients should be given the strength of AIRTIDE containing the appropriate fluticasone propionate dosage for the severity of their disease.
If the patient can not be controlled adequately with inhaled corticosteroid therapy alone, replacement of the therapy with therapeutically equivalent corticosteroid dose AIRTIDE may improve asthma control. Replacement of treatment with ARTIDE in asthmatic patients who can only be controlled adequately with inhaled corticosteroid therapy may result in a reduction in the dose of corticosteroids while maintaining asthma control. Please see the Pharmacodynamic properties section for more details.

Recommended Doses:

Adolescents 12 years and older:
Twice a day, 1 inhalation (50 microgram salmeterol ve 100 microgram fluticasone propionate) or twice a day, 1 inhalation (50 microgram salmeterol ve 250 microgram fluticasone propionate) or twice a day, 1 inhalation (50 microgram salmeterol ve 500 microgram fluticasone propionate)

In adult or adolescent patients with moderate persistent asthma (defined according to the patient's daily symptoms, daily rescue medication use and moderate to severe airway limitation) who require rapid control, a short course of AIRTIDE may be considered as initial therapy. In these cases, the recommended starting dose is 50 micrograms salmeterol and 100 micrograms fluticasone propionate as two inhalations twice daily. Once asthma control is achieved, treatment should be reviewed and patients should be considered for dose reduction to inhaled corticosteroids alone. It is important that patients are followed up regularly while the dose is being reduced.

When one or two disease severity criteria are missing, no clear benefit has been shown compared to the use of inhaled fluticasone propionate alone as initial treatment. Overall, inhaled corticosteroids remain the first-line treatment in the vast majority of patients. AIRTIDE is not intended for the initial treatment of mild asthma. AIRTIDE 50 microgram / 100 microgram doses are not suitable for use in children and adults with severe asthma; it is important to demonstrate the appropriate dose of inhaled corticosteroids before using any fixed combination in patients with severe asthma.

Chronic Obstructive Pulmonary Disease (COPD)
Adults: Twice a day 1 inhalation 50/250 microgram-50/500 microgram salmeterol/ fluticasone propionate.
Method of administration:
AIRTIDE is for inhalation use only.

Patients should be instructed to use their inhaler correctly. During inhalation, the patient should preferably be standing or upright sitting position.

Additional information for specific populations:
Renal/Hepatic Failure:
There is no need to adjust the dose.

Paediatric population
There are no data available for use of AIRTIDE in children aged under 4 years.

In children aged 4 -12 years:
1 inhalation (50 microgram salmeterol and 100 microgram fluticasone propionate) 2 times a day.

Geriatric population:
There is no need to adjust the dose.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients of AIRTIDE listed in section 6.1.

4.4 Special warnings and precautions for use

The active substance salmeterol should not be used as monotherapy alone in patients with asthma.

AIRTIDE is not recommended for mild asthma treatment.

Worsening of the disease
When using long-acting β2 agonists such as salmeterol contained in AIRTIDE, patients should be closely monitored for the first three months after starting this drug, especially in terms of asthma-related adverse events.
AIRTIDE should not be used to treat acute asthma symptoms for which a fast- and short- acting bronchodilator is required. Patients should be advised to have their inhaler to be used for relief in an acute asthma attack available at all times.

Treatment should not be started with long-acting beta-agonists if the patients are in exacerbation periods or if they have severe or acutely worse asthmatic complaints.

Serious adverse effects or exacerbations associated with asthma may occur during treatment with AIRTIDE. Patients should be instructed that if their asthma symptoms are uncontrolled or worsen after initiation of treatment with AIRTIDE, they should continue treatment but still consult their physician.

Increased requirements for use of reliever medication (short-acting bronchodilators), or decreased response to reliever medication indicate deterioration of control and patients should be reviewed by a physician.

Rarely, serious and sometimes fatal asthma-related breathing problems may occur due to long-acting beta-agonist preparations.

In pediatric and adolescent patients using long-acting beta-agonists in addition to inhaled corticosteroids, a combination preparation containing both an inhaled corticosteroid and a long-acting beta-agonist is recommended to ensure compliance with both drugs.

Long-acting beta-agonists should be used in the shortest time to control asthma symptom and should be stopped if asthma control is achieved. Patients should then be treated with a controlled treatment.

The sudden and progressive deterioration of asthma control is a life threatening condition and the patient must be examined again by the physician. An increase in the dose of corticosteroids should be considered.

If exacerbation is associated with an infection in patients with asthma or COPD, additional corticosteroid therapy and antibiotic administration should be considered.

AIRTIDE treatment in patients with asthma should not be stopped abruptly due to risk of exacerbation, treatment dosage should be reduced gradually under physician control. For patients with COPD cessation of therapy may also be associated with symptomatic decompensation and should be supervised by a physician.

Once asthma symptoms are under control, a gradual reduction of the dose of AIRTIDE may be considered. It is important that patients are monitored regularly while treatment is gradually reduced. The lowest effective dose of AIRTIDE should be used (see section 4.2).

As with all inhaled medicines containing corticosteroids, AIRTIDE should be used with caution in patients with active or silent pulmonary tuberculosis and in patients with fungal, viral or other respiratory infections. Appropriate treatment should be initiated immediately if necessary.

Cardiovascular effects
At high therapeutic doses, AIRTIDE may infrequently cause cardiac arrhythmias (e.g. supraventricular tachycardia, extrasystole and atrial fibrillation) and transient mild decreases in serum potassium levels. AIRTIDE should be used with caution in patients with serious cardiovascular disorders or cardiac arrhythmias and in patients with diabetes mellitus, thyrotoxicosis, untreated hypokalemia or predisposition to low serum potassium levels.

Hyperglycemia
Very rarely, increased blood glucose levels have been reported (see section 4.8) and this should be taken into account when prescribing to patients with a history of diabetes mellitus.

Paradoxical bronchospasm
As with other inhalation therapies, paradoxical bronchospasm with increased wheezing and shortness of breath may occur immediately after dose administration. Paradoxical bronchospasm responds to a fast-acting bronchodilator and should be treated immediately. AIRTIDE should be discontinued immediately, the patient should be evaluated and alternative treatment should be initiated if necessary.

Pharmacologic side effects of β2 agonist therapy such as tremor, palpitations and headache have been reported, but these tend to be transient and decrease with regular treatment.

Systemic corticosteroid effects
Systemic effects may occur when any inhaled corticosteroid is used for a long time, especially at high doses. These effects are much less likely to occur than with oral corticosteroid administration (see section 4.9 Overdosage). Possible systemic effects include Cushing's syndrome, Cushing's-like symptoms, adrenal suppression, delayed growth in children and adolescents, decreased bone mineral density, cataracts and glaucoma and, less commonly, psychological and behavioral effects such as psychomotor hyperactivity, sleep disturbance, anxiety, depression and aggression (especially in children). It is therefore important to regularly assess treatment in patients with asthma and adjust the dose of inhaled corticosteroids to the lowest dose that provides effective control.

Long-term treatment of patients with high doses of inhaled corticosteroids can cause adrenal suppression and acute adrenal crisis. At doses of 500 to 1000 micrograms fluticasone propionate, there have been very rare reports of adrenal suppression and acute adrenal crises. Conditions that could potentially trigger an acute adrenal crisis include trauma, surgery, infection or sudden reductions in dose. The symptoms observed are often vague but include anorexia, abdominal pain, weight loss, fatigue, headache, nausea, vomiting, hypotension, decreased level of consciousness, hypoglycemia and seizures. Additional systemic choritcosteroid therapy should be considered during stress or elective surgery.

Inhaled fluticasone propionate therapy is expected to minimize the need for oral steroids, but patients transferred from oral steroids may be at risk of adrenal insufficiency for a significant period of time. Therefore, such patients should be followed closely and adrenocorticol function should be monitored. This risk may also be present in patients with a history of emergency high dose corticosteroid treatment. The possibility of impaired adrenal response should always be kept in mind in emergency and elective situations likely to cause stress and appropriate corticosteroid treatment should be considered. The degree of adrenal insufficiency may require specialist assessment before elective procedures.

Ritonavir can greatly increase the concentration of fluticasone propionate in plasma. Concomitant use should therefore be avoided unless the potential benefit to the patient outweighs the side effects of systemic corticosteroids. The risk of systemic side effects is also increased when fluticasone propionate is used in combination with other strong CYP3A inhibitors.
Clinical evidence of the advantage of high dose use in COPD is inadequate.

Pneumonia in COPD patients
An increased incidence of pneumonia, including pneumonia requiring hospitalization, has been observed in COPD patients receiving inhaled medicines containing corticosteroids. There is evidence of an increased risk of pneumonia with increasing steroid dose, but this has not been conclusively demonstrated in all studies.

There is no definitive clinical evidence for intra-class variation in the magnitude of the risk of pneumonia with corticosteroid-containing inhaled medicines.

Physicians should be alert to the possible development of pneumonia in COPD patients due to the possibility of confounding the clinical features of infections with exacerbation of COPD symptoms.
Risk factors for pneumonia in COPD patients include smoking, older age, low body mass index and severe COPD.

Interaction with CYP3A4 inhibitors
Concomitant use with systemic ketoconazole significantly increases systemic exposure to salmetorol. This may result in an increased incidence of systemic effects (e.g. prolonged QTc interval and palpitations). Concomitant use with CYP3A4 inhibitors should therefore be avoided unless the potential benefit to the patient outweighs the risk of systemic salmeterol side effects.

Visual disturbances
Visual disturbances may be reported with systemic and topical corticosteroid use. If a patient complains of blurred vision or other visual disturbances, the patient should be referred to an ophthalmologist for evaluation of possible causes such as cataracts, glaucoma or central serous chorioretinopathy (CSCR) reported after systemic and topical corticosteroid use.

Pediatric population
Children and adolescents under 16 years of age receiving high doses of fluticasone propionate (usually 1000 micrograms/day or more) may be at risk. Systemic effects may occur, especially with long-term treatment at high doses. Possible systemic effects include Cushing's syndrome, Cushing's-like symptoms, adrenal suppression, acute adrenal crisis, delayed growth in children and adolescents and, less commonly, psychomotor hyperactivity, sleep disturbance, anxiety, depression and aggression. Referral of the child or adolescent patient to a pediatric respiratory specialist should be considered.

Regular height monitoring of children receiving long-term inhaled corticosteroid therapy is recommended. Inhaled corticosteroids should be used at the lowest dose that provides asthma control.

Excipients:
Each dose of AIRTIDE contains up to 12.3275 milligrams of lactose monohydrate. This amount does not normally cause problems in people with lactose intolerance. The lactose excipient contains small amounts of milk protein, which may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

β adrenergic blockers may weaken or antagonize the effect of salmeterol. The use of both non-selective and selective β blockers should be avoided in asthmatic patients unless there are compelling reasons for their use. Potentially severe hypokalemia can occur with β2 agonist therapy. In acute severe asthma, special caution is advised as this effect may be increased by concomitant treatment with xanthine derivatives, steroids and diuretics.

Concomitant use of other β-adrenergic containing drugs may have a potentially additive effect.

Fluticasone Propionate
Under normal conditions, after inhalation administration, the plasma concentration of fluticasone propionate is low as a result of extensive first-pass metabolism and high systemic clearance mediated by cytochrome P450 3A4 in the liver and intestine. Therefore, clinically significant drug interactions mediated by fluticasone propionate are unlikely.

A drug interaction study in healthy volunteers showed that ritonavir (a highly potent cytochrome CYP3A4 inhibitor), 100 mg twice daily, was able to increase plasma concentrations of fluticasone propionate several hundred-fold and led to a significant decrease in serum cortisol concentrations. There is no information on this interaction for inhaled fluticasone propionate, but A significant increase in fluticasone propionate plasma levels is expected. Cases of Cushing's syndrome and adrenal suppression have been reported. Therefore, concomitant use of ritonavir and fluticasone propionate should be avoided unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects.

In a small-scale study in healthy volunteers, ketoconazole, a lower potency CYP3A inhibitor, increased fluticasone propionate exposure by 150% after a single inhalation. This effect resulted in a greater decrease in plasma cortisol levels than fluticasone propionate alone. Concomitant treatment with other potent CYP3A inhibitors such as itraconazole and cobicistat-containing drugs and moderately potent CYP3A inhibitors such as erythromycin is also expected to increase systemic fluticasone propionate exposure and the risk of systemic side effects. Concomitant use should be avoided unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects. Patients should be monitored for systemic corticosteroid side effects in concomitant use.

Salmeterol
Strong CYP3A4 inhibitors
In a 7-day drug interaction study in 15 healthy volunteers, concomitant systemic ketoconazole (400 mg once daily) and salmeterol (50 micrograms inhaled twice daily) significantly increased plasma salmeterol exposure (Cmax 1.4-fold and AUC 15-fold). This may result in an increased incidence of other systemic effects of salmeterol treatment (e.g. QTc interval prolongation and palpitations) compared with salmeterol or ketoconazole treatment alone.

Clinically significant effects on blood pressure, heart rate, blood glucose and blood potassium levels were not observed. Co-administration with ketoconazole did not increase salmeterol elimination half-life or salmeterol accumulation with repeated dosing.

Concomitant use with ketoconazole should be avoided unless the benefits of treatment outweigh the risk of increased systemic side effects of salmeterol. There is likely to be a similar risk of interaction with other potent CYP3A4 inhibitors (e.g. itraconazole, telithromycin, ritonavir).

Moderate CYP 3A4 inhibitors
Co-administration of salmeterol (50 micrograms twice daily by inhalation) and erythromycin (500 mg orally once daily) for 6 days in 15 healthy volunteers resulted in a small but not statistically significant increase in salmeterol exposure (Cmax 1.4-fold and AUC 1.2-fold). Co-administration of erythromycin has not been associated with any serious adverse effects.

Additional information for special populations
Interaction studies have not been performed in elderly patients or in patients with renal or hepatic impairment (see section 5.2).

Pediatric population:
Interaction studies have not been performed in pediatric patients (see section 5.2).

4.6 Pregnancy and Lactation

General Recommendation
Pregnancy category: C

Fertile women / Contraception
There are no data in humans.

Pregnancy
There is not enough data on the use in pregnancy. Studies on animals have shown that reproductive toxicity exists (see Section 5.3). The potential risk for humans is unknown.
Reproductive toxicity studies on animals with drugs in the form of single drugs or combinations elicit the expected fetal effects of excessive beta 2 adrenoceptor agonists and glucocorticosteroids at extreme systemic exposure levels.
Administration of Seretide to pregnant women should only be considered if the expected benefit to the mother is greater than any possible risk to the fetus.

Data from pregnant women (more than 1000 pregnant cases) do not show malformation or feto/neonatal toxicity of salmeterol and fluticasone propionate. Animal studies have shown reproductive toxicity after administration of β2 adrenoreceptor agonists and glucocorticosteroids.

In pregnant women, the lowest effective dose of fluticasone propionate that provides asthma control should be used.

Breastfeeding
It is not known whether salmeterol and fluticasone propionate/metabolites are excreted in human milk.

Studies have shown that salmeterol and fluticasone propionate and their metabolites are excreted in the milk of lactating rats.

The risk in breastfeeding newborns/infants cannot be ruled out. Considering the benefit of breastfeeding for the child and the benefit of treatment for the mother, it should be decided whether to discontinue AIRTIDE treatment or breastfeeding.

Fertility
There are no data on its use in humans. However, animal studies have shown that salmeterol or fluticasone treatment has no effect on fertility.

4.7 Effects on ability to drive and use machines

There is no specific study of the effects of AIRTIDE ond riving and use machines, but the pharmacology of both medicines suggests there will be no effect.

4.8. Undesirable effects

As AIRTIDE contains salmeterol and fluticasone propionate, the type and severity of adverse reactions associated with each of the compounds may be expected. There is no incidence of additional adverse events following concurrent administration of the two compounds.

Adverse drug reactions related to salmeterol / fluticasone propionate is classified by The Med DRA System Organ Class. Frequency categories are defined as follows:

Very common ≥1/10
Common ≥1/100 to <1/10
Uncommon ≥1/1,000 to <1/100
Rare ≥1/10,000 to <1/1,000
Very rare <1/10,000
Unknown (cannot be estimated with the available data)

Infections & Infestations
Common :Candidiasis of the mouth and throat, pneumonia, (in COPD patients), bronchitis
Rare :Esophageal candidiasis

Immune System Disorders
Uncommon: Cutaneous hypersensitivity reactions, respiratory symptoms (dyspnea)
Very rare: Angioedema (mainly facial and oropharyngeal oedema), respiratory symptoms (bronchospasm, anaphylactic reactions including anaphylactic shock

Endocrine Disorders:
Very rare[4]: Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, decreased bone mineral density, cataract,

Metabolism & Nutrition Disorders:
Common: Hypokalaemia
Very rare: Hyperglycaemia

Psychiatric Disorders:
Uncommon: Anxiety, sleep disorders
Rare: Behavioral changes, including psychomotor hyperactivity and irritability (mostly in children)
Unknown: Depression, aggression (predominantly in children)

Nervous System Disorders:
Very common: Headache
Common: Tremor

Eye Disorders:
Uncommon :Cataract
Rare :Glaucoma
Unknown :Blurred vision

Cardiac Disorders:

Uncommon: Palpitations, Tachycardia, atrial fibrillation, angina pectoris
Very rare: Cardiac arrhythmias (including supraventricular tachycardia and extrasystoles).

Respiratory, Thoracic & Mediastinal Disorders
Very common: Nasopharyngitis
Common: Throat irritation, hoarseness/dysphonia, sinusitis
Very rare: Paradoxical bronchospasm

Skin and subcutaneous tissue disorders:
Common: Contusions

Musculoskeletal & Connective Tissue Disorders

Common: Muscle cramps, traumatic fractures, Arthralgia, myalgia

Description of selected adverse events
Pharmacologic side effects of β2 agonist treatment such as tremor, palpitations and headache have been reported, but these tend to be transient and decrease with regular treatment.

As with other inhalation therapies, paradoxical bronchospasm with increased wheezing and shortness of breath may occur immediately after dose administration. Paradoxical bronchospasm responds to a fast-acting bronchodilator and should be treated immediately. AIRTIDE should be discontinued immediately, the patient should be evaluated and alternative treatment should be initiated if necessary.

Due to the fluticasone propionate content, hoarseness, oral and throat candidiasis (thrush) and, in rare cases, esophageal candidiasis (thrush) may occur in some patients. Both hoarseness and the incidence of candidiasis of the mouth and throat can be relieved by washing the mouth and/or brushing the teeth after use of the product. Symptomatic candidiasis of the mouth and throat may be treated with topical anti-fungal therapy while treatment with AIRTIDE is ongoing.

Additional information on special populations:
Pediatric population
Possible systemic effects include Cushing's syndrome, Cushing's-like symptoms, adrenal suppression and delayed growth in children and adolescents (see section 4.4). Children may also experience anxiety, sleep disturbance and behavioral changes such as hyperactivity and irritability.

Reporting of side effects
If you get any side effects, stated or not stated in the Patient Information Leaflet, talk to your doctor or pharmacist. Also, please report the side effects you have to Turkish Pharmacovigilance Center (TÜFAM) by either clicking to "Reporting Drug Side Effect" icon on www.titck.gov.tr or calling side effect reporting line via 0 800 314 00 08. By reporting the side effects you can help provide more information on the safety of this medicine.

TÜFAM	Turkish Pharmacovigilance Center www.titck.gov.tr

4.9 Overdose and Treatment

Symptoms and signs
There are no clinical study data on overdose for AIRTIDE, but overdose information on salmeterol and/or fluticasone propionate is given below:

Signs and symptoms of salmeterol overdose include drowsiness, increased systolic blood pressure, tremor, headache and tachycardia. There is no specific treatment for AIRTIDE overdose. In case of overdose, the patient should be given supportive treatment with appropriate observation as needed. In addition, hypokalemia may occur, therefore serum potassium levels should be monitored. Potassium replacement should be considered.

Acute: Acute inhalation of higher than recommended doses of fluticasone propionate may cause transient suppression of adrenal function. This dose does not require immediate treatment as adrenal function returns to normal within a few days as confirmed by plasma cortisol measurements.

Chronic overdose with inhaled fluticasone propionate:
Adrenal reserve should be monitored. Treatment with systemic corticosteroids may be necessary. When stabilization is achieved, treatment with inhaled corticosteroids at the recommended dose should be continued. For adrenal suppression, see section 4.4.
In both acute and chronic fluticasone propionate overdose, AIRTIDE treatment should be continued at the appropriate dosage for symptom control.

5.PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: R03A K06

Pharmacotherapeutic group: Adrenergic inhalants (selective beta-2 adrenergic receptor agonists) and other inhalants (corticosteroids)

Mechanism of action
AIRTIDE contains salmeterol and fluticasone propionate which have differing modes of action. While salmeterol protects against the indication, fluticasone propionate improves lung function and prevents exacerbations. AIRTIDE may offer a more suitable regimen for patients who are receiving concurrent beta-agonist and inhaled corticosteroid therapy. The mechanisms of action of both drugs are given below:

Salmeterol
Salmeterol is a selective long-acting (12 hour) β_2 adrenoceptor agonist with a long side chain which binds to the exo-site of the receptor.
Salmeterol provide longer-lasting bronchodilatation that lasts at least 12 hours, based on the recommended doses of conventional short-acting beta$_2$-agonists.

Fluticasone propionate is a glucocorticoid that acts as a powerful antiinflammatory agent in the lungs when given at the recommended doses by inhalation and reduces symptoms and exacerbations of asthma without side effects observed with systemically administered corticosteroids.

Clinical efficacy and safety
Fluticasone propionate/Salmeterol asthma clinical trials
A 12-month study (Achieving Optimal Asthma Control, GOAL) in 3416 adults and adolescents with long-term asthma compared the efficacy and safety of inhaled corticosteroids (Fluticasone Propionate) alone with Fluticasone Propionate/Salmeterol to determine whether asthma treatment goals were achievable. The treatment dose was increased every 12 weeks until **Total control was achieved or the highest dose of study drug was reached. GOAL showed that asthma control was achieved in more patients given fluticasone propionate/Salmeterol than in patients given inhaled corticosteroids (ICS) alone, and that this control was achieved at a lower dose of corticosteroids.
*Well-controlled asthma was achieved more quickly with Fluticasone propionate/Salmeterol compared to ICS alone. The duration of treatment in 50% of patients to achieve an individual week of well-controlled asthma was 16 days for Fluticasone propionate/Salmeterol and 37 days for the IKS group. In a subgroup of patients with no previous steroid treatment, the time to an individually well-controlled week was 16 days with Fluticasone propionate/Salmeterol and 23 days with ICS.

The overall study findings showed the following:

Proportion of Patients with *Well Controlled (WC) and **Not Totally Controlled (TC) Asthma at 12 Months				
Pre-Study Treatment	Salmeterol/FP		FP	
	WC	TC	WC	TC
No ICS (short-acting beta agonist SABA alone)	%78	% 50	%70	%40
Low dose ICS (≤500mcg beclomethasone dipropionate (BDP) or equivalent/day)	%75	%44	%60	%28
Medium dose ICS (>500-1000mcg dipropyanate BDP or equivalent/day)	%62	%29	%47	%16
Combined findings at the 3 treatment level	%71	%41	%59	%28

*Adequately controlled asthma; ≤ 2 days with a symptom score of >1 (symptom score 1 is defined as 'one brief symptom during the day'), ≤2 days and ≤4 SABA use per week, ≥ 80% predicted morning peak expiratory flow, absence of nocturnal awakenings, absence of exacerbations, and absence of side effects requiring treatment change

**Fully controlled asthma; absence of symptoms, absence of SABA use, ≥ 80% predicted morning peak expiratory flow, absence of nocturnal awakenings, absence of exacerbations and absence of side effects requiring treatment change

The findings in this study suggest that twice-daily doses of Salmeterol/Fluticasone 50/100 micrograms may be considered as initial maintenance therapy in patients with moderate to severe refractory asthma in whom rapid asthma control is considered necessary.

A double-blind, randomized, parallel-group, double-blind, randomized, parallel-group study in 318 patients aged ≥18 years with refractory asthma evaluated the safety and tolerability of Fluticasone propionate/Salmeterol in two inhalations (double dose) twice daily over a two-week period. This study showed that doubling each Fluticasone propionate/Salmeterol dose inhalation for up to 14 days was associated with a small increase in beta agonist-related side effects (tremor; 0 vs. 1 patient [1%], palpitations; 1 patient [<1%] vs 6 [3%], muscle cramps; 1 patient [<1%] vs 6 [3%]) and a similar incidence of inhaled corticosteroid-related side effects (e.g. oral candidiasis; 16 patients [8%] vs 6 [6%], hoarseness; 4 patients [2%] vs 2 [2%]). The small increase in beta agonist-related side effects should be taken into account when considering doubling the dose of fluticasone propionate/Salmeterol in adult patients requiring additional short-term (up to 14 days) inhaled corticosteroid therapy.

Asthma

Multicenter Salmeterol Asthma Research Study

The Multicenter Salmeterol Asthma Research Study was a 28-week US study comparing the safety of adding salmeterol or placebo to usual treatment in adult and adolescent volunteers. Although there was no significant difference in the primary endpoint, the combined number of respiratory-related deaths and respiratory-related life-threatening events, the study showed a significant increase in the number of asthma-related deaths in patients receiving salmeterol (13 deaths in 13,176 patients treated with salmeterol compared to 13 deaths in 13,179 patients receiving placebo). The study was not designed to assess the effect of concomitant use of inhaled corticosteroids and only 47% of volunteers reported the use of ICS at baseline.

Safety and efficacy of salmeterol plus fluticasone propionate versus fluticasone propionate alone in asthma effectiveness

Two multicenter 26-week studies were conducted to compare the safety and efficacy of salmeterol+fluticasone propionate with fluticasone propionate alone, one in adult and adolescent volunteers (the AUSTRI study) and one in pediatric volunteers aged 4-11 years (the VESTRI study). Subjects included in both studies had moderate to severe persistent asthma with asthma-related hospitalization or asthma exacerbation in the previous year. The primary objective of both studies was to assess the non-inferiority of adding LABA (salmeterol+fluticasone propionate) to ICS therapy (salmeterol+fluticasone propionate) compared to ICS alone (fluticasone propionate) in terms of asthma-related events (asthma-related hospitalization, endotracheal intubation and death). The secondary objective of the study was to assess the superiority of ICS+LABA (salmeterol+fluticasone propionate) over ICS alone (fluticasone propionate) in terms of severe asthma exacerbation (defined as worsening of asthma requiring systemic corticosteroid use for at least 3 days or asthma-related hospitalization or emergency department admission requiring systemic corticosteroid use).

The AUSTRI and VESTRI studies randomized and treated 11,679 and 6,208 patients, respectively. For the primary endpoint of safety, both studies showed non-inferiority (see table below)

Serious events with asthma at 26 weeks AUSTRI and VESTRI

	AUSTRI		VESTRI	
	Salmeterol+ Fluticasone propionate (n=5.834)	Fluticasone propionate only (n=5.845)	Salmeterol+ Fluticasone propionate (n=3.107)	Fluticasone propionate only (n=3.101)
Combined endpoint (asthma-related hospitalization, endotracheal intubation and death)	34 (%0.6)	33 (%0.6)	27 (%0.9)	21 (%0.7)
Salmeterol+fluticasone propionate/fluticasone propionate risk ratio (GA: %95)	1.029 (0.638-1.622)a		1.285 (0.726-2.272)b	
Death	0	0	0	0
Asthma-related hospitalization	34	33	27	21
hospitalization				
Endotracheal intubation	0	2	0	0

[a] If the upper 95% CI for relative risk is less than 2.0, decide on a non-inferiority conclusion given

[b] If the upper 95% CI for relative risk is less than 2.675, non-inferiority was judged

For the secondary efficacy endpoint, a reduction in time to first asthma exacerbation was seen in salmeterol+fluticasone propionate compared with fluticasone propionate in both studies, but only in AUSTRI was the difference statistically significant:

	AUSTRI		VESTRI	
	Salmeterol+ Fluticasone propionate (n=5.834)	Fluticasone propionate only (n=5.845)	Salmeterol+ Fluticasone propionate (n=3.107)	Fluticasone propionate only (n=3.101)

Number of volunteers with asthma exacerbations	480 (%8)	597 (%10)	265 (%9)	309 (%10)
Salmeterol+fluticasone propionate/fluticasone propionate risk ratio (CI: %95)	0.787 (0.698, 0.888)		0.859 (0.729, 1.012)	

COPD

Symptomatic COPD patients without a 10% reversibility restriction to short-acting beta2-agonists:
Placebo-controlled clinical trials conducted over 6 months showed that regular use of 50/250 micrograms and 50/500 micrograms of Fluticasone propionate/Salmeterol rapidly and significantly improved lung function and significantly reduced shortness of breath and the use of reliever medication. There was also a significant improvement in the patients' health status.

Symptomatic COPD patients with less than 10% reversibility to short-acting beta2-agonists:
Placebo-controlled clinical trials conducted over 6 and 12 months showed that regular use of 50/500 micrograms Fluticasone propionate/Salmeterol rapidly and significantly improved lung function and significantly reduced shortness of breath and the use of reliever medication. Over a 12-month period, the risk of COPD exacerbation and the need for additional oral corticosteroids were significantly reduced. There was also a significant improvement in the patients' health status.

Fluticasone propionate/Salmeterol 50/500 micrograms was effective in improving lung function and health status and reducing the risk of COPD exacerbations in both on-treatment smokers and patients who had stopped smoking.

The TORCH study (Towards a Revolution in COPD Health): TORCH is a 3-year study to evaluate the effect of treatment with 50/500 micrograms of fluticasone propionate/salmeterol twice daily, 50 micrograms of salmeterol twice daily, 500 micrograms of FP (fluticasone propionate) twice daily or placebo on all-cause mortality in patients with COPD. Patients with moderate-to-severe and severe COPD with baseline (before bronchodilator) FEV1 less than 60% of the expected normal value were randomized to receive double-blind treatm
ent. Throughout the study, they were allowed to receive their usual COPD treatment, except for other inhaled corticosteroids, long-acting bronchodilators and long-acting systemic corticosteroids. 3-year survival was determined for all patients regardless of whether they exited the study. The primary endpoint was a reduction in all-cause mortality at 3 years for Fluticasone propionate/Salmeterol compared to placebo (Table 1).

Table1

	Plasebo N = 1524	Salmeterol 50 N = 1521	FP 500 N = 1534	Fluticasone propionate/ Salmeterol 50/500 N = 1533
All-cause mortality in 3 years				
Number of deaths (%)	231 (% 15.2)	205 (% 13.5)	246 (% 16.0)	193 (% 12.6)
Risk ratio against placebo (GA) p value	Not applicable	0.879 (0.73, 1.06) 0.180	1.060 (0.89, 1.27) 0.525	0.825 (0.68, 1.00) 0.0521
Risk ratio, components versus Fluticasone propionate/Salmeterol 50/500 (GA) p value	Not applicable	0.932 (0.77, 1.13) 0.481	0.774 (0.64, 0.93) 0.007	Not applicable

Adjusted P value for a log-rank analysis of 2 interim analyses of the 1st primary efficacy comparison, stratified by smoking status.

Fluticasone propionate/Salmeterol was shown to reduce the risk of death at any time within 3 years by 17.5% compared to placebo (Risk Ratio 0.825 (95% CI 0.68, 1.00, p = 0.052; all adjusted for interim analyses). Compared to placebo, there was a 12% reduction in deaths from any cause at any time over the three-year period with salmeterol (p = 0.180) and a 6% increase with FP (p = 0.525). (Table 1)

A supporting analysis using Cox's Proportional Hazards model showed a risk ratio of 0.811 (95% CI 0.670, 0.982, p = 0.031) for Fluticasone propionate/Salmeterol showing a 19% reduction in the risk of death at any time within 3 years compared to placebo. The model was adjusted for important factors (smoking status, age, gender, region, baseline FEV1 and Body Mass Index). There was no evidence that treatment effects varied by these factors (Table 1).

The percentage of patients who died from COPD-related causes over three years was 6% for placebo, 6.1% for salmeterol, 6.9% for FP and 4.7% for fluticasone propionate/salmeterol (Table 1). (Table 1)
Fluticasone propionate/Salmeterol reduced moderate to severe exacerbations by 25% (95% CI: between 19% and 31%; p < 0.001) compared to placebo Fluticasone propionate/Salmeterol reduced the exacerbation rate by 12% (95% CI: between 5% and 19%; p = 0.002) compared to salmeterol and by 9% (95% CI: between 1% and 16%; p = 0.024) compared to FP. Compared to placebo, salmeterol and FP significantly reduced the exacerbation rate by 15% (95% CI: between 7% and 22%; p < 0.001) and 18% (95% CI: between 11% and 24%; p < 0.001), respectively.

Health-Related Quality of Life, as measured by the St George Respiratory Survey (SGSA), improved with all active treatment modalities compared to placebo. The mean improvement with Fluticasone propionate/Salmeterol compared to placebo over three years was - 3.1 units (95% CI: between - 4.1 and - 2.1; p <0.001), compared to salmeterol - 2.2 units (p < 0.001) and compared to FP - 1.2 units (p = 0.017). Over the three-year treatment period, FEV1 values were higher in those treated with Fluticasone

propionate/Salmeterol than in those treated with placebo (mean difference over 3 years 92 mL, 95% CI: 75 - 108 mL; p < 0.001). Fluticasone propionate/Salmeterol was more effective than salmeterol or FP on FEV1 (mean difference for salmeterol was 50 mL, p < 0.001 and 44 mL for FP, p < 0.001).

The estimated 3-year probability of pneumonia reported as an adverse event was 12.3% for placebo, 13.3% for salmeterol, 18.3% for FP and 19.6% for Fluticasone propionate/Salmeterol (risk ratio of Fluticasone propionate/Salmeterol versus placebo: 1.64, 95% CI: between 1.33 and 2.01, p < 0.001). There was no increase in pneumonia-related deaths; deaths considered to be primarily due to pneumonia during treatment were 7 for placebo, 9 for salmeterol, 13 for FP and 8 for Fluticasone propionate/Salmeterol. There was no significant difference in the likelihood of bone fracture (placebo 5.1%, salmeterol 5.1%, FP 5.4% and Fluticasone propionate/Salmeterol 6.3%; risk ratio for Fluticasone propionate/Salmeterol versus placebo: 1.22, 95% CI: between 0.87 and 1.72, p = 0.248). The incidence of adverse events related to eye disorders, bone disorders and hypothalamic-pituitary-adrenal axis disorders was low and did not differ between treatments. There is no evidence of an increase in cardiac adverse events in treatment groups receiving salmeterol.

Pediatric population:
In the SAM101667 study, in 158 children aged 6 to 16 years with symptomatic asthma, the combination of salmeterol/fluticasone propionate was equally effective as doubling the dose of fluticasone propionate for symptom control and lung function. This study was not designed to investigate effects on exacerbation.

In a 12-week study of children aged 4 to 11 years (n=257) treated with salmeterol/fluticasone propionate 50/100 or salmeterol 50mcg + fluticasone propionate 100mcg, both twice daily, a 14% improvement in peak expiratory flow and improvements in symptom score and salvage salbutamol use were seen in both treatment arms. No differences were found between the two treatment arms. There were no differences in safety parameters between the two treatment arms.

Safety was the primary objective in a randomized parallel group study of children (n=203) aged 4 to 11 years with persistent asthma who were symptomatic while on inhaled corticosteroid treatment. Children received salmeterol/fluticasone propionate alone (50/100mcg) or fluticasone propionate alone (100mcg) twice daily. Two children receiving salmeterol/fluticasone propionate and five children receiving fluticasone propionate dropped out of the study due to worsening of asthma. At the end of 12 weeks, there were no children with abnormal 24-hour urinary cortisol excretion in either arm of the study. There was no difference in the safety profile between the task force.

Use of fluticasone propionate-containing medicines in asthma during pregnancy
To assess the risk of major congenital malformations (MCMs), an observational retrospective epidemiologic cohort study comparing first trimester exposure to inhaled inhaled fluticasone propionate alone and salmeterol+fluticasone propionate versus ICS without fluticasone propionate was conducted using UK electronic health records. This study did not include placebo for comparison.

In an asthma cohort of 5362 pregnant women with first trimester ICS-exposure, 131 diagnosed CCMs were identified; 42 of 1612 (30%) with fluticasone propionate or salmeterol+fluticasone propionate exposure were diagnosed with CCMs. At 1 year, the adjusted odds ratio for diagnosed CCMs in women comparing fluticasone propionate versus non-fluticasone propionate ICS exposure was 1,.1 (95% CI: 0.5 to 2.3) in moderate asthmatics and 1.2 (95% CI: 0.7 to 2.0) in severe asthmatics. There was no difference in the risk of MCM when comparing exposure to fluticasone propionate alone with salmeterol plus fluticasone propionate in the first trimester. Across asthma severity grades, absolute risks of MI ranged from 2.0 to 2.9 per 100 pregnancies exposed to fluticasone propionate. This was comparable to the results

of a study of 15,840 pregnancies without exposure to asthma treatment in the General Practice Research Database (2.8 MCMs per 100 pregnancies).

5.2 Pharmacokinetic properties

There is no evidence that salmeterol and fluticasone propionate administered in combination in animals and in humans through inhalation affect each other's pharmacokinetics.

For this reason, in terms of pharmacokinetics, both components can be considered separately.

Salmeterol
Salmeterol acts locally in the lung therefore plasma levels are not an indication of therapeutic effects. In addition there are only limited data available on the pharmacokinetics of salmeterol because of the technical difficulty of assaying the drug in plasma due to the low plasma concentrations at therapeutic doses (approximately 200 picogram /mL or less) achieved after inhaled dosing.

Fluticasone propionate

Absorption:
The absolute bioavailability of fluticasone propionate for each inhaler device was calculated by comparing the inhalation or intravenous pharmacokinetic data between the study and the study. Absolute bioavailability in healthy adult subjects ranges from 5 to 11%. Fluticasone propionate in patients with asthma or COPD has been found to have less systemic exposure. Systemic absorption occurs primarily from the lungs and is rapid at the beginning and then slowing down. The remaining inhaled dose can be ingested, but the systemic exposure has little to do with the edible part due to low water solubility and presystemic elimination resulting in less than 1% oral bioavailability. A linear increase in systemic exposure is achieved by increasing the dose.

Distribution:

Fluticasone propionate
The rate of binding of fluticasone propionate to plasma proteins is moderately high (91%). The distribution in steady state is large.
The disposition of fluticasone propionate is characterized by high plasma clearance (1150 ml/min), high volume of distribution at steady state (300 L) and a terminal half-life of approximately 8 hours.

Biotranformation:

Fluticasone propionate
Fluticasone propionate is metabolized to inactive carboxylic acid mainly by the cytochrome P450 enzyme CYP3A4.

Elimination:

Fluticasone propionate is cleared very rapidly from the systemic circulation. Renal clearance of fluticasone propionate clearance is negligible. Less than 5% of the dose is excreted in the urine mainly as metabolites. Most of the dose is excreted in feces as metabolites and unchanged.

Characteristic features in patients

Renal/Hepatic Failure:
No data available.

Different age groups:

- Pediatric population
- In a population pharmacokinetics analysis using data reported from 9 studies involving 350 patients aged 4 to 77 years (174 patients aged 4-11 years), using different devices (DISKUS, metered inhaler) and including control groups, higher systemic exposure to fluticasone propionate was seen following treatment with Fluticasone propionate/Salmeterol 50/100 compared with fluticasone propionate 100.
-
- Geometric Mean Ratio [90% CI] for fluticasone propionate versus Salmeterol/fluticasone propionate in Children and Adolescent/Adult Populations

Treatment (test versus reference)	***Population***	***EAA***	***C_{maks}***
Salmeterol/ fluticasone propionate 50/100 fluticasone propionate 100	*Children (4 -11 years)*	*1.20 [1.06 – 1.37]*	*1.25 [1.11 – 1.41]*
Salmeterol/ fluticasone propionate 50/100 fluticasone propionate 100	*Adolescent/Adult (≥12 years)*	*1.52 [1.08 – 2.13]*	*1.52 [1.08 – 2.16]*

- The effect of 21-day treatment with Fluticasone propionate/Salmeterol inhaler 25/50 micrograms (2 inhalations twice daily with or without a spacer) or Fluticasone propionate/Salmeterol 50/100 micrograms (1 inhalation twice daily) was evaluated in 31 children aged 4 to 11 years with mild asthma. Systemic exposure to salmeterol was similar for fluticasone propionate/Salmeterol inhaler, fluticasone propionate/Salmeterol inhaler with spacer and fluticasone propionate/Salmeterol (126pg h/mL [95% GA: 70, 225], 103pg h/mL [95% GA: 54, 200] and 110 pg h/mL [95% GA: 55, 219], respectively). Fluticasone propionate systemic exposure was higher with the Fluticasone propionate/Salmeterol inhaler used in combination with a spacer (107pg h/mL [95% GA: 45.7, 252. 2]) and Fluticasone propionate/Salmeterol (138pg h/mL [95% GA: 69.3, 273.2]), but lower for Fluticasone propionate/Salmeterol inhaler (24pg h/mL [95% GA: 9.6, 60.2]).

5.3 Preclinical safety data

Based on animal studies of salmeterol and fluticasone propionate administered separately, the only safety concern for use in humans was effects associated with increased pharmacological potency.

In animal reproduction studies, glucocorticoids have been associated with malformations (cleft palate, skeletal disorders) have been shown to be caused. However, these animal studies are not considered to be relevant for humans given the recommended doses. Animal studies with salmeterol xinafoate have shown embryofetal toxicity only at high exposure levels. An increased incidence of transposed umbilical artery and incomplete oscification of the ossipital bone was found in rats at doses associated with known glucocorticoid-induced anomalies following co-administration. Salmeterol xinafoate or fluticasone propioynate did not show the potential for genetic toxicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Lactose monohydrate (cow milk sourced)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

It must be stored at room temperature below 25 ° C. It should be stored in a dry place.
Keep out of the sight and reach of children and in its packaging.

6.5 Nature and contents of container

It is sold in carton boxes containing 60 capsules HDPE bottles and an inhalation device.

6.6 Special precautions for disposal and other handling

All unused products and residuals should be disposed of in accordance with the "Medical Waste Control Regulation" and "Packaging and Packaging Waste Control Regulation".

AIRTIDE released dust from the lungs is released.

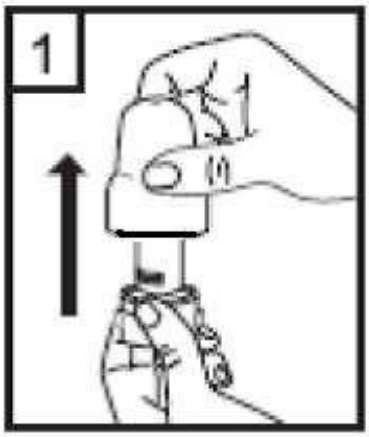
The use of the inhalation device should be shown to the patient by the doctor and the pharmacist. The patient should be informed that the capsules should never be ingested into the mouth and swallowed after

being placed in the inhaler. The patient should be told that the gelatin capsule can be disintegrated and the oral and bovine small gelatin particles can reach after inhalation. This probability is reduced to a minimum by more than one puncture of the capsule.

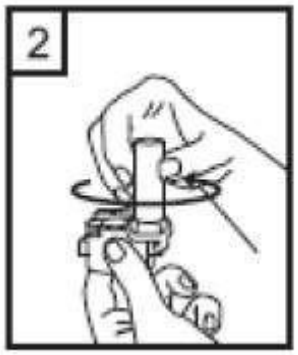
The appliance is opened by removing the protective cover and the handling is prepared. The mouthpiece is placed in place and the lips are closed to surround it. After that the dose can be inhaled and the guard can be closed again.

Instructions for use of AIRTIDE

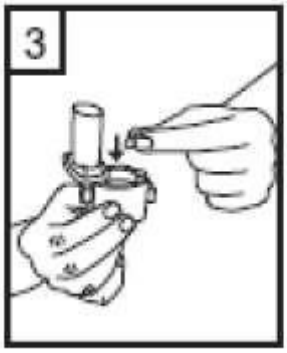
1. Pull out the lid.



2. Hold the lower part of the appliance with one hand and open the mouthpiece with the other hand by turning it in the direction of the arrow.



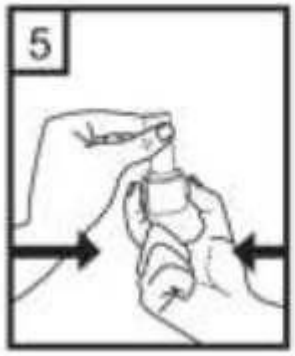
3. Place a capsule in the opening in the device. Remove the capsule immediately before using it.



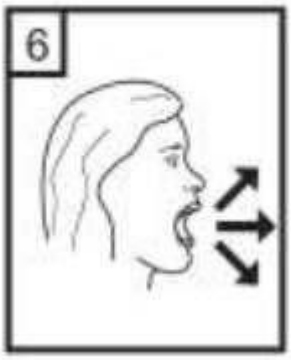
4. Close the mouthpiece by turning it.

5. Keep the appliance upright, press and release the buttons on the side only once exactly. The capsule will be pierced from both ends.

During your breathing, you may come to your mouth with small pieces of gelatin capsules. The gelatinous components are harmless and will be digested after being swallowed. The risk of the formation of small pieces of gelatin is removed from the packaging of the capsule, can not be removed immediately, and is reduced by pressing the buttons only once.



6. Give your breath out.



7. Place the mouthpiece in your mouth and tilt your head slightly backwards. Close your lips tightly around the mouthpiece and breathe as fast and deep as you can.

8. Remove the appliance from your mouth and hold your breath for as long as possible without discomfort. Then breathe normally. Turn the device on again and check that there is no dust inside the capsule. If there is dust in the capsule, repeat steps 6, 7 and 8.

9. After use, throw empty capsules and close the mouthpiece.

DO NOT FORGET!

Keep your device dry.

Keep it closed when not in use.

Never breathe into the appliance.

Push it when you are only ready to take the pill.

Do not take more than the mentioned dose.

7. MARKETING AUTHORIZATION HOLDER

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Mahmutbey Mahallesi, Tasocagi Yolu
Caddesi, Solen Residance Apt.No:19/1/11
Bagcilar/Istanbul/TURKEY

8. MARKETING AUTHORIZATION NUMBER

2016/840

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

28.11.2016

10. DATE OF THE REVISION OF THE TEXT

09.03.2022