SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

AIRTIDE 100mcg/50 mcg Capsules for Inhalation

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:
Within each inhalation capsule:

salmeterol xinafoate*	72.5 mcg
fluticasone propionate	100 mcg

*equal to 50 mcg salmeterol

Excipients:

Lactose monohydrate	12.32 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.

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:
Children 4 years and older:
Twice a day, 1 inhalation (50 microgram salmeterol and 100 microgram fluticasone propionate)

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)

Adults 18 years and older:
In adults, up to 14 days twice the dose of all AIRTIDE doses and twice daily dosing are comparable safety and tolerability, which can be considered when patients need additional short-term inhaled corticosteroid therapy (up to 14 days), as shown in asthma treatment guidelines.

Chronic Obstructive Pulmonary Disease (COPD)
Adults: Twice a day 1 inhalation 50/250 microgram-50/500 microgram salmeterol/ fluticasone propionate. A maximum dose of 50/500 micrograms of AIRTIDE taken twice daily has been shown to reduce all-cause mortality (see Section 5.2).

Method of administration:
AIRTIDE is for inhalation use only.

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.

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

In asthma treatment, a gradual program should normally be followed and the response of the patient should be monitored clinically and with lung function tests.
AIRTIDE is not recommended for mild asthma treatment.

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.

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.

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. The patient must be re-examined by the physician in cases where the current dose of AIRTIDE can not control asthma adequately.

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.

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.

Clinical evidence of the advantage of high dose use in COPD is inadequate.

The incidence of pneumonia has increased in patients with COPD receiving AIRTIDE (See section 4.8). Physicians should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of exacerbations overlap with the clinical properties of pneumonia.

As with all inhaled medication containing corticosteroids, AIRTIDEshould be administered with caution in patients with active or quiescent pulmonary tuberculosis and fungal, viral or other infections of the airway.

AIRTIDE should be used wit caution in patients with thyrotoxicosis.

Cardiovascular effects such as increased systolic blood pressure and increased heart rate may be seen with all sympathomimetic drugs, especially when administered at higher doses than therapeutic doses.
Systemic effects may occur with any inhaled corticosteroid, particularly at high doses prescribed for long periods. These effects are much less likely to occur than with oral corticosteroids (See section 4.9). Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression, delay in the growth of children and adolescents, decrease in bone mineral density, cataract and glaucoma. It is important, therefore, that the dose of inhaled corticosteroid is reduced to the lowest dose at which effective control of asthma is maintained.

The possibility of impaired adrenal response in stressful and urgent emergency situations should always be kept in mind and proper corticosteroid therapy should be considered (see sections 4.9).

It is recommended that children who have been treated for a long time with inhaled corticosteroid treatment regularly monitor their height.
Some individuals may show more sensitivity to corticosteroids more than other patients.

Due to the possibility of inadequate adrenal response, patients who are switched to oral fluticasone propionate therapy from oral steroid therapy should be closely monitored and adrenal function should be monitored regularly. After the cessation of systemic corticosteroids, it takes several months for the hypothalamic pituitary adrenal axis (HPA) functions to improve. Patients whose systemic steroid therapy has been discontinued in stress and severe asthma attacks should be instructed to start oral corticosteroid therapy again and urgently consult physicians. When the inhaled fluticasone propionate therapy is initiated, the systemic steroid dose should be gradually reduced and patients should be encouraged to have steroid alert card shipments indicating that additional treatment may be required at stress times.

When the inhaled fluticasone propionate therapy is initiated, the systemic steroid dose should be gradually reduced and patients should be encouraged to have steroid alert card shipments indicating that additional treatment may be required at stress times.

There have been very rare reports of increases in blood glucose levels (see section 4.8) and this should be considered when prescribing to patients with a history of diabetes mellitus.
Depending on long-acting beta-agonist preparations, respiratory problems related to asthma, which may be rare, serious and sometimes fatal, may occur. A large study in the US called SMART compared salmeterol (a component of salmeterol-fluticasone propionate) or placebo with standard treatment and a significant increase in asthma-related deaths was observed in patients receiving salmeterol compared to the results obtained. Data from a large clinical trial suggested African-American patients were at increased risk of serious respiratory-related events or deaths when using salmeterol compared with placebo. It is not known if this was due to pharmacogenetic or other factors. The SMART study was not designed to determine whether the use of concurrent corticosteroids via inhalation increases the risk of asthma-related death.(See section 5.1). In pediatric and adolescent patients who use long-acting beta-agonists in addition to infusion corticosteroids, it is recommended to use a combination preparation containing both the induction corticosteroid and the long-acting beta agonist to guarantee both compliance.

4.5 Interaction with other medicinal products and other forms of interaction

Both non-selective and selective β blockers should be avoided unless there are compelling reasons for their use.
Concomitant use of other β adrenergic containing drugs can have a potentially additive effect.
Under normal circumstances, low plasma concentrations of fluticasone propionate are achieved after

inhaled dosing, due to extensive first pass metabolism and high systemic clearance mediated by cytochrome P450 3A4 in the gut and liver. Hence, clinically significant drug interactions mediated by fluticasone propionate are unlikely.
In an interaction study in healthy subjects with intranasal fluticasone propionate, ritonavir (a highly potent cytochrome P450 3A4 inhibitor) 100 mg b.i.d. increased the fluticasone propionate plasma concentrations several hundred fold, resulting in markedly reduced serum cortisol concentrations. Clinically significant drug interactions have been reported in patients receiving intranasal or inhale fluticasone propionate and ritonavir during post-marketing, resulting in systemic corticosteroid effects including Cushing's syndrome and adrenal suppression. Therefore, concomitant use of ritonavir and fluticasone propionate should be avoided unless the potential benefit to the patient is greater than the risk of systemic corticosteroid side effects.

Studies have shown that other cytochrome P450 3A4 inhibitors cause negligible (erythromycin) and small (ketoconazole) increases in systemic exposure to fluticasone propionate without a significant reduction in serum cortisol concentrations. However, caution should be exercised when fluticasone propionate is used in combination with potent P450 3A4 inhibitors (eg, ketoconazole), as systemic exposure potential increases.
In a drug interaction study, concurrent systemic ketoconazole use significantly increased plasma salmeterol exposure. (Cmax 1.4 fold and AUC 15 fold) This may lead to prolongation of QTc interval (See section 5.2). Caution should be exercised when administering strong CYP3A4 inhibitors (eg ketoconazole) and salmeterol together.

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

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.
Extensive clinical experience with drugs in this class has not provided evidence that their effects are related to therapeutic doses. Neither salmeterol xinafoate nor fluticasone propionate has been shown to possess a genetic toxicity potency. It should not be used during pregnancy unless it is necessary.

Breastfeeding
Experience with the use of salmeterol xinafoate and fluticasone propionate during pregnancy and breastfeeding is inadequate. It should preferably not be used during breastfeeding.

Salmeterol excreted in breast milk. Plasma levels of salmeterol and fluticasone propionate, both of which are induced at therapeutic doses, are very low, and accordingly concentrations in the mother's milk are likely to be low. This was supported by studies on lactating animals that measured low drug concentrations in the column.

Fertility
No data available.

4.7 Effects on ability to drive and use machines

There is no specific study of the effects of AİRTIDE 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.
As with other inhalation therapy paradoxical bronchospasm may occur with an immediate increase in wheezing and shortness of breath after dosing. Paradoxical bronchospasm responds to a rapid-acting bronchodilator and should be treated straightaway. AIRTIDE should be discontinued immediately, the patient assessed and alternative therapy instituted if necessary.

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)

Very common and common events are usually determined from clinical trial data. Rare and very rare events are usually based on spontaneous data.

Infections & Infestations
Common: Candidiasis of the mouth and throat, Pneumonia, Bronchitis

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

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

Metabolism & Nutrition Disorders:

Common: Hypokalaemia
Very rare: Hyperglycaemia

Psychiatric Disorders:
Very rare: Anxiety, sleep disorders and behavioural changes include hyperactivity and irritability (predominantly in children)
Unknown: Depression, aggression (predominantly in children)

Nervous System Disorders:
Very common: Headache
Common: Tremor

Cardiac Disorders:
Common: Palpitations
Uncommon: Tachycardia
Very rare: Cardiac arrhythmias (including supraventricular tachycardia and extrasystoles).

Respiratory, Thoracic & Mediastinal Disorders
Very common: Nasopharyngitis
Common: Throat irritation, hoarseness/dysphonia, sinusitis, pneumonia (in COPD patients)
Very rare: Paradoxical bronchospasm

Skin and subcutaneous tissue disorders:
Common: Contusions

Musculoskeletal & Connective Tissue Disorders
Common: Muscle cramps, traumatic fractures
Very rare: Arthralgia, myalgia

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
The overdosage information for AIRTIDE, salmeterol and /or fluticasone propionate is given below:

Symptoms and signs expected by overdose of salmeterol are due to typical excessive beta2-adrenergic stimulation such as tremor, headache, tachycardia, and increases in systolic blood pressure and hypokalaemia. Acute inhalation at doses exceeding the approved doses of fluticasone propionate may temporarily lead to suppression of the hypothalamus-pituitary-adrenal axis. This does not require immediate action; adrenal function returns to normal in a few days.

Adrenocortical suppression may occur at a significant rate if doses on the approved AIRTIDE dose are continued for extended periods of time. There are very few reports of acute adrenal crises in children who have been exposed to a prolonged period of time (several months or years), especially over approved dose. Conditions such as exposure to trauma, surgical intervention, infection, or rapid decline in the dose of inhale fluticasone propionate are the conditions that will trigger an acute adrenal crisis.
Patients are not advised to use AIRTIDE at doses above the approved doses. It is important to regularly monitor treatment and to reduce the minimum approved dose to provide effective control of the disease (see Section 4.2)

Treatment
Preferred antidotes are cardioselective beta-blockers that should be used with caution in patients with a history of bronchospasm. If treatment of AIRTIDE should be discontinued due to overdose of the beta-agonist component of the drug, initiation of appropriate corticosteroid replacement therapy should be considered.

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.
These pharmacological properties of salmeterol inhibit histamine-induced bronchoconstriction more effectively and provide longer-lasting bronchodilatation that lasts at least 12 hours, based on the recommended doses of conventional short-acting beta2-agonists.
In vitro tests have shown that salmeterol is a potent and long-lasting inhibitor of mast cell mediated release of histamine, leukotrienes and prostaglandin D2 in human lungs.
In situ, salmeterol inhibits early and late phase responses to allergens induced; the late phase response inhibitory effect lasts for 30 hours following a single dose, even when the bronchodilator effect has ended.A single salmeterol dose reduces bronchial hyperresponsiveness. These characteristics indicate that salmeterol is in addition to non-bronchodilator activity, but this effect has not been fully clarified clinically. This mechanism is different from the anti-inflammatory action mechanism of corticosteroids.

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.
During chronic treatment with the inhale fluticasone propionate, daily adrenocortical hormone release

remains within normal limits, even at the highest recommended doses for children and adults. After the exceed of fluticasone propionate from other inhaled steroids, the release of daily adrenocortical hormones has been gradually and evenly reversed despite the intermittent use of oral steroids, thus demonstrating the conversion of the adrenal fluticasone propionate to normal adrenal function values. The adrenal reserve also remains normal during chronic treatment, as measured by a normal increase in the stimulation test. However, it should be taken into account that any residual adrenal deficit from the previous treatment can persist for a considerable period of time (see Section 4.4).

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.

Co-administration of ketoconazole which is CYP3A4 inhibitor (400 mg orally once daily) and salmeterol (50 micrograms inhaled twice daily) in 15 healthy subjects for 7 days resulted in a significant increase in plasma salmeterol exposure (1.4-fold Cmax and 15-fold AUC)

There is no increase in salmeterol accumulation with repeated dosing.
Three patients were discontinued with salmeterol and ketoconazole because of QTc prolongation or palpitations accompanied by sinus tachycardia. Administration of salmeterol and ketoconazole in the remaining 12 subjects did not have a clinically meaningful effect on heart rate, blood potassium or QTc interval (see Section 4.4 and Section 4.5)

Absorption:

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. Following regular use of salmeterol xinafoate, hydroxynaphthoic acid is detectable in the systemic circulation and steady-state concentrations reach approximately 100 ng / ml. These concentrations are 1000 times lower than the steady-state concentrations observed in toxicity studies. No harmful effects have been observed in long-term regular use (over 12 months) in patients with airway obstruction.

Fluticasone propionate
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:

Salmeterol

The binding rate of salmeterol to plasma proteins is 96%.

Fluticasone propionate

The rate of binding of fluticasone propionate to plasma proteins is moderately high (91%). The distribution in steady state is large.

Biotranformation:

Salmeterol

An in vitro study has shown that salmeterol was metabolized by cytochrome P450 3A4 (CYP3A4) to alpha-hydroxysalmeter (aliphatic oxidation) largely.

Fluticasone propionate

Fluticasone propionate is mainly cleansed from the systemic circulation by metabolizing the inactive carboxylic acid by the cytochrome P450 enzyme CYP3A4. Caution should be exercised when systemic exposure to fluticasone propionate is potentially increased when used in combination with agents known as CYP3A4 inhibitors.

Elimination:

Salmeterol

The elimination half life is 5.5 hours. Salmeterol 60% is excreted in stool and 25% is excreted in urine.

Fluticasone propionate

The disposition of fluticasone propionate is characterised by high plasma clearance (1150 mL/min), and a terminal half-life of approximately 8 hours. The renal clearance of fluticasone propionate is negligible (<0.2%) and less than 5% is in the form of metabolites.

Characteristic features in patients

Renal/Hepatic Failure:

No data available.

Different age groups:

Population pharmacokinetic analysis was performed using data from asthmatic patients (9 for fluticasone propionate (FP) and 5 clinical studies for salmeterol) and showed below:

- Compared with FP alone (100 mcg), higher FP exposure was observed in adolescents and adults ratio 1.52 [90% *CI* 1.08, 2.13] and children (ratio 1.20 [90% *CI* 1.06, 1.37] after administration of Salmeterol / Fluticasone (50/100 mcg)
- Higher FP exposure was observed in children receiving Salmeterol / Fluticasone (50/100 mcg) compared to adolescents and adults (ratio 1.63 [90% *CI* 1.35, 1.96]
- The clinical significance of these findings is unknown, but no difference was observed between the effects on the hypothalamus-pituitary-adrenal axis in both adolescents and adults and children in clinical studies involving Salmeterol / Fluticasone (50/100 mcg) and FP (100 mcg) for 12 weeks.
- When higher dose (50/500 micrograms) of Salmeterol / Fluticasone was taken, FP exposure compared to equivalent FP doses applied alone was found to be similar.
- Higher salmeterol exposure was observed in children receiving Salmeterol / Fluticasone (50/100 micrograms) compared to adolescents and adults (ratio 1.23 [90% *CI* 1.10, 1.38]

- The clinical significance of these findings is unknown, but there has been no difference in cardiovascular effects or tremor reports among adults, adolescents, and children during studies of up to 12 weeks.

Clinical Studies

Clinical studies with salmeterol

Asthma
The Salmeterol Multi-center Asthma Research Trial (SMART) is a large-scale study in the United States comparing safety of salmeterol or placebo with standard treatment. There are no significant differences at the primer endpoint (combined respiratory-related death and life-threatening events associated with respiration). This study showed a significant increase in asthma-related deaths in patients receiving salmeterol (13 deaths in 13,176 patients in the salmeterol group versus 3 deaths in 13,179 patients in the placebo group at 28 weeks). This study was not designed to assess the effect of concurrent corticosteroid use via inhalation. Post-hoc analyzes, however, did not show a significant difference between the treatment groups in terms of asthma-related mortality (patients 3/6138 versus 4/6127 in the salmeterol group) for patients who initially used steroids taken by inhalation. The number of asthma-related deaths in the non-steroid treated groups by inhalation was 9/7049 in the salmeterol group and 0/7041 in the placebo group. In addition, a meta-analysis of 42 clinical trials involving 8030 patients on the Salmeterol-FP and 7925 patients on fluticasone propionate did not show a statistical difference between salmeterol-FP and fluticasone propionate in terms of hospitalization due to severe respiratory-related events or asthma.

Clinical Trials with Salmeterol / Fluticasone powder for inhalation:

Asthma
A twelve month study (Gaining Optimal Asthma ControL, GOAL), in 3416 adult and adolescent patients with persistent asthma, compared the safety and efficacy of Salmeterol/Fluticasone powder versus inhaled corticosteroid (Fluticasone Propionate) alone to determine whether the goals of asthma management were achievable. Treatment was stepped up every 12 weeks until **total control was achieved or the highest dose of study drug was reached. The control had to continue at least 7 of the last 8 weeks of treatment.
In this study, the following results were obtained:

- Only 59% of patients treated with inhaled corticosteroids achieved "good control", this rate was 71% in patients using Salmeterol / Fluticasone Inhalation powder.
- Only 28% of patients treated with inhaled corticosteroids reached "full control" level, this rate was 41% in patients using Salmeterol / Fluticasone Inhalation powder.

These effects were seen with the Salmeterol / Fluticasone Inhalation Powder at an earlier and lower dose of the corticosteroid compared to the inhaled corticosteroids alone.
Following results were achieved in the GOAL study:
* Exacerbation rate with Salmeterol / Fluticasone Inhalation Powder is 29% lower when compared to only inhaled corticosteroid therapy.

* Achieving "good control" and "full control" status in asthma control has increased the Quality of Life. Salmeterol / Fluticasone for Inhalation After treatment with powder, 61% of patients reported that their quality of life was "minimally impaired" or "never deteriorated". This effect, which was initially 8%, was measured by the asthma-specific quality of life questionnaire.

"Well-controlled asthma": Rare symptoms or rarely use of short-acting beta-agonists, or lung function is less than 80% of what is expected. No nocturnal waking, no exacerbation, and no side effects that require a change in treatment.

"Fully controlled asthma": no symptoms, no short-acting beta-agonist use, lung function equal to or greater than 80% of expected, no waking at night, no exacerbation, no side effects that require a change in treatment.

Salmeterol / Fluticasone Inhalation Improvement in pulmonary function and improvement in percentage of days without symptoms, reduction in rescue medication use and use of 60% lower inhaled corticosteroid doses were observed in two other studies when compared with the use of inhaled corticosteroids alone at the lower level measured by bronchial biopsy and bronchoalveolar lavage the control of the underlying airway inflammation was also persistent.

Additional studies have shown that Salmeterol / Fluticasone Inhalation Powder significantly alleviates asthma symptoms and lung function and reduces the use of salvage medication when compared to individual components of Salmeterol / Fluticasone Inhalation Powder and individualized placebo. The results of the GOAL study showed that the healing with salmeterol / fluticasone Inhalation Powder lasts at least 12 months at these end points.

COPD
Symptomatic COPD patients without 10% reversibilty restriction to short-acting beta2-agonists:
Placebo-controlled clinical trials conducted over a six-month period showed that regular use of 50/250 micrograms and 50/500 micrograms Salmeterol / Fluticasone Inhalation Powder reduced lung function at a rapid and significant level, significantly reducing respiratory distress and relieving drug use. At the same time, there was a significant improvement in the health status of the patients.

Symptomatic COPD patients with less than 10% reversibility of short-acting beta2-agonists:
Placebo-controlled clinical trials for 6 and 12 months showed that regular use of 50/500 micrograms Salmeterol / Fluticasone Inhalation powder improves pulmonary function rapidly and significantly at a significant rate, significantly reducing breathlessness and relieving drug use. During the 12-month period, the risk of exacerbation of COPD and the need for additional oral corticosteroids decreased significantly. At the same time, there was a significant improvement in the health status of the patients.

Salmeterol / Fluticasone Inhalation Powder 50/500 micrograms are used in both smokers and in patients who quit smoking improved lung function and health status, and reduced COPD exacerbation risk.

TORCH study (TOwards Revolution in COPD Health):
TORCH was designed to assess the effect of treatment with all-cause mortality of 50/500 micrograms Salmeterol / Fluticasone Inhalation Powder 2 times daily, 50 micrograms salmeterol 2 times daily, 500 micrograms FP (fluticasone propionate) or placebo twice a day in patients with COPD, It is a 3 year study . Moderate-severe COPD patients with FEV1 less than 60% of the expected normal value (prior to bronchodilator) were randomized to receive double-blind treatment. During the study, they were allowed to take regular COPD treatments, except for other trafficking corticosteroids, long-acting bronchodilators, and prolonged systemic corticosteroids. Three-year survival was determined for all patients, regardless of whether they left the clinic or not. The main end point is reduction of all-cause mortality for Salmeterol / Fluticasone Inhalation Powder over 3 years compared to placebo (Table 1).

Table 1

	Placebo N=1524	*Salmeterol 50 N=1521*	*FP 500 N=1534*	*Salmeterol/ Fluticasone Inhalation Powder 50/500 N=1533*
All cause mortality at 3 years				
Number of deaths (%)	*231 (15.2%)*	*205 (13.5%)*	*246 (16.0%)*	*193 (12.6%)*
Hazard Ratio vs Placebo (CIs) p value	*N/A*	*0.879 (0.73,1.06) 0.180*	*1.060 (0.89, 1.27) 0.525*	*0.825 (0.68, 1.00) 0.052*[1]
Hazard Ratio Salmeterol/ Fluticasone Inhalation Powder 50/500 (CIs) *p value*	*N/A*	*0.932 (0.77, 1.13) 0.481*	*0.774 (0.64, 0.93) 0.007*	*N/A*

1. Non-significant P value after adjustment for 2 interim analyses on the primary efficacy comparison from a log-rank analysis stratified by smoking status.

Salmeterol / Fluticasone reduced the risk of death at any time by 17.5% within 3 years compared with placebo (Risk ratio 0.825 (95% CI 0.68, 1.00, p = 0.052, all set for interim analysis).
Compared to placebo, deaths that occurred at any time during the three year period had a 12% reduction with salmeterol (p = 0.180) and a 6% increase with FP (p = 0.525).

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

The percentage of patients who died of COPD-related causes within 3 years was 6.0% for placebo, 6.1% for salmeterol, 6.9% for FP and 4.7% for Salmeterol / Fluticasone Inhalation Powder (Table 1)

Compared to the placebo, Salmeterol / Fluticasone Inhalation Powder reduced moderate to severe exacerbations by 25% (95% CI: 19% and 31%, p <0.001). Salmeterol / Fluticasone reduced the rate of exacerbation by 12% (95% CI between 5% and 19%, p = 0.002) when compared to salmeterol and by 9% when compared to FP(95% CI between 1% and 16%, p = 0.024).

Compared with placebo, salmeterol and FP reduced the rate of exacerbations to 15% (95% CI between 7% and 22%, p <0.001) and 18% (95% CI between 11% and 24%, p <0.001), respectively, at significant levels.

The Health Related Quality of Life measured by the St George Respiratory Questionnaire (SGSA) was improved by all active treatment methods compared to placebo.The mean improvement achieved with Salmeterol / Fluticasone Inhalation Powder over three years was -3.1 units (95% CI : between -4.1 and -

2.1; p< 0.001) compared to placebo, -2.2 units(p< 0.001 compared to salmeter and -1.2 units (p=0.017)compared to FP.

During the three-year treatment period, FEV1 values are higher those treated with Salmeterol / Fluticasone Inhalation Powder than treated with placebo. (Mean difference over 3 years was 92 ml, 95% CI: 75-108 ml; p < 0.001). Salmeterol / Fluticasone Inhalation Powder is more effective than salmeterol or FP in correcting FEV1. (Mean difference for salmeterol is 50 ml, p <0.001 and 44 ml for FP, p <0.001).

The 3-year predicted probability of adverse event reported as pneumonia is 12.3% for placebo, 13.3% for salmeterol, 18.3% for FP and 19.6% for salmeterol / fluticasone Inhalation Powder.
The risk ratio of salmeterol / fluticasone to placebo: 1.64, 95% CI: 1.33 and 2.01, p < 0.001).
There was no increase in deaths associated with pneumonia; deaths that were considered to be primarily due to pneumonia during treatment were 7 for placebo, 9 for salmeterol, 13 for FP and 8 for salmeterol / fluticasone Inhalation Powder. There is no significant difference in the probability of bone fracture (placebo 5.1%, salmeterol 5.1%, FP 5.4%, Salmeterol / Fluticasone Inhalation Powder 6.3%, risk for placebo versus Salmeterol/fluticasone inhalation powder: 1.22, 95% CI: 0.87 and 1.72 , p = 0.248).

The incidence of adverse events related to ocular disorders, bone disorders and hypothalamic-pituitary-adrenal axis disorders is low and there is no difference between treatments. There is no evidence that there is an increase in cardiac adverse events in salmeterol receiving treatment groups.

5.3 Preclinical safety data

Salmeterol xinafoate and fluticasone propionate have been evaluated extensively in toxicity tests on animals. Significant toxicity occurs only when the recommended doses are exceeded for human use and are consistent with the effects expected with the use of potent beta2-adrenoreceptor agonists and glucocorticosteroids.

For a long time, salmeterol led to the formation of benign tumors in the smooth muscle of the xenophate rat mesothelium and mouse uterus.

Rodents are susceptible to the formation of these pharmacologically induced tumors. Salmeterol is not thought to pose a significant risk to the oncogenic path in humans.

Coadministration of salmeterol and fluticasone propionate at high doses has led to some cardiovascular interactions. Mild atrial myocarditis and focal coronary arteritis in rats are transient effects that improve with the administration of normal doses. Compared to the administration of salmeterol alone in dogs, the increase in heart rate is greater after co-administration.
In animals, co-administration practices did not cause a change in other toxicities associated with drug classes.

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.

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".

"Do not throw away drugs that have expired or are not in use! Give to the collection system determined by the Ministry of Environment and Urbanism. "

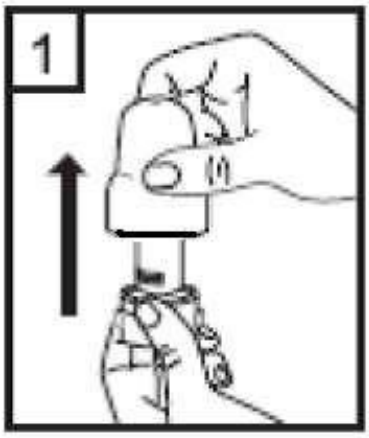
AIRTIDE released dust from the lungs is released.

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.

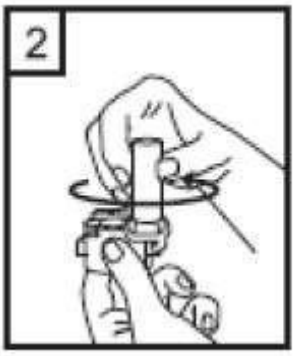
The appliance is opened by removing the protective cover and the handling is prepared. The mouthpiece is placed in place and the lips are closed to surround it. After that the dose can be inhaled and the guard can be closed again.

Instructions for use of AIRTIDE

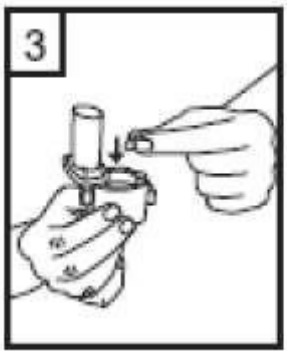
1. Pull out the lid.



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.



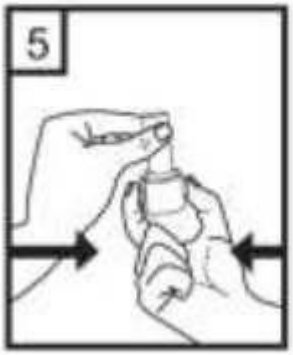
3. Place a capsule in the opening in the device. Remove the capsule immediately before using it.



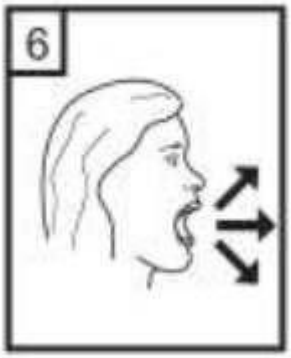
4. Close the mouthpiece by turning it.

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

Humanis Saglik A.S.
Mahmutbey Mah. Tasocagi Yolu Caddesi Solen Residance Apt. No:19/1/11
Bagcilar-Istanbul/TURKEY

8. MARKETING AUTHORIZATION NUMBER

2016/838

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

28.11.2016

10. DATE OF THE REVISION OF THE TEXT