1 NAME OF THE MEDICINAL PRODUCT & PHARMACEUTICAL FORM

ZENHALE® 50/5

(mometasone furoate 50 mcg and formoterol fumarate dihydrate 5 mcg) pressurized inhalation suspension [inhalation aerosol]

ZENHALE® 100/5

(mometasone furoate 100 mcg and formoterol fumarate dihydrate 5 mcg) pressurized inhalation suspension [inhalation aerosol]

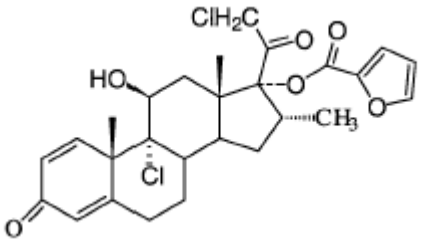
ZENHALE® 200/5

(mometasone furoate 200 mcg and formoterol fumarate dihydrate 5 mcg) pressurized inhalation suspension [inhalation aerosol]

Description

Mometasone furoate

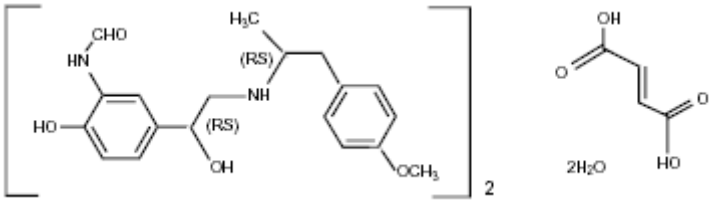
Mometasone furoate is a synthetic, anti-inflammatory corticosteroid with a chemical name of 9,21-dichloro-11 β ,17-dihydroxy-16 α -methylpregna-1,4-diene-3,20-dione 17-(2)-furoate with the following chemical structure:



Mometasone furoate has a molecular weight of 521.44 and its empirical formula is $C_{27}H_{30}Cl_2O_6$.

Formoterol fumarate

Formoterol fumarate dihydrate, a racemate, is a selective beta$_2$-adrenergic bronchodilator with a chemical name of (±)-2-hydroxy-5-[(1RS)-1-hydroxy-2-[[(1RS)-2-(4-methoxyphenyl)-1-methylethyl]-amino]ethyl]formanilide fumarate dihydrate with the following chemical structure:



Formoterol fumarate dihydrate has a molecular weight of 840.9, and its empirical formula is $(C_{19}H_{24}N_2O_4)_2 \cdot C_4H_4O_4 \cdot 2H_2O$.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

ZENHALE 50/5 delivers 50 mcg of mometasone furoate and 5 mcg of formoterol fumarate dihydrate per actuation.

ZENHALE 100/5 delivers 100 mcg of mometasone furoate and 5 mcg of formoterol fumarate dihydrate per actuation.

ZENHALE 200/5 delivers 200 mcg of mometasone furoate and 5 mcg of formoterol fumarate dihydrate per actuation.

For a full list of excipients, see section 3.1 List of Excipients of Special Interest

3 PHARMACEUTICAL PARTICULARS

3.1 List of Excipients of Special Interest

Hydrofluoroalkane (HFA-227)
Anhydrous Alcohol
Oleic Acid

3.2 Incompatibilities

N/A

3.3 Instructions for Use and Handling and Disposal

ZENHALE should be primed before using for the first time by releasing 4 test sprays into the air, away from the face, shaking well before each spray. In cases where the inhaler has not been used for more than 5 days, prime the inhaler again by releasing 4 test sprays into the air, away from the face, shaking well before each spray.

Shake well prior to each inhalation.

The canister should not be removed from the actuator because the correct amount of medication may not be discharged; the dose counter may not function properly; reinsertion may cause the dose counter to count down by 1 and discharge a puff.

3.4 Instructions for Cleaning the ZENHALE Inhaler

The mouthpiece should be cleaned using a dry wipe after every 7 days of use.

Routine cleaning instructions:

- Remove the cap off the mouthpiece. Wipe the inside and outside surfaces of the actuator mouthpiece with a clean, dry lint-free tissue or cloth. Put the cap back on the mouthpiece after cleaning.
- Do not attempt to unblock the actuator with a sharp object, such as a pin.
- Do not wash or put any parts of the inhaler in water.

The correct amount of medication in each inhalation cannot be ensured after the labeled number of actuations from the canister has been used, even though the inhaler may not feel completely empty and may continue to operate. The inhaler should be discarded when the labeled number of actuations has been used (the dose counter will read “0”).

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

ZENHALE, administered twice daily, is indicated for the maintenance treatment of asthma, in adults and children 12 years of age and older with reversible obstructive airway disease, whose asthma cannot be adequately controlled on asthma controller medications.

ZENHALE is not indicated for patients whose asthma can be managed by occasional use of a rapid onset, short duration, inhaled $beta_2$-agonist or for patients whose asthma can be successfully managed by inhaled corticosteroids along with occasional use of a rapid onset, short duration, inhaled $beta_2$-agonist.

ZENHALE should be used for patients not adequately controlled with inhaled corticosteroids and "as needed" inhaled short-acting $beta_2$-agonists or whose disease severity clearly warrants initiation of treatment with two maintenance therapies.

ZENHALE may also be used in patients already adequately controlled on both inhaled corticosteroid and long-acting beta$_2$-agonist.

ZENHALE contains a long-acting beta$_2$-agonist and should not be used as a rescue medication. To relieve acute asthmatic symptoms, a rapid onset, short duration inhaled bronchodilator (e.g., salbutamol) should be used.

Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue **ZENHALE**) if possible without loss of asthma control, and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use **ZENHALE** for patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids.

4.2 Posology and Method of Administration

4.2.1 General

ZENHALE should be administered by oral inhalation only. After each dose, patients should be advised to rinse their mouth with water and spit out the contents without swallowing.

The cap from the mouthpiece of the actuator should be removed before using **ZENHALE**.

The **ZENHALE** canister should only be used with the **ZENHALE** actuator. The **ZENHALE** actuator should not be used with any other inhalation drug product. Actuators from other products should not be used with the **ZENHALE** canister.

4.2.2 Dose

ZENHALE should be administered as two inhalations twice daily (morning and evening) by oral inhalation.

When choosing the starting dosage strength of **ZENHALE**, consider the patient's disease severity, based on their previous asthma therapy, including the inhaled corticosteroid dosage, as well as the patient's current control of asthma symptoms and risk of future exacerbation.

For patients whose asthma is currently controlled, the recommended dose for **ZENHALE** treatment based on prior asthma therapy is provided in the table below.

Table 1: Recommended Dosages for ZENHALE		
Previous Therapy	**Recommended Dose**	**Maximum Recommended Daily Dose**

Inhaled low dose corticosteroids	**ZENHALE** 50/5, 2 inhalations twice daily	200/20 microgram
Inhaled medium dose corticosteroids	**ZENHALE** 100/5, 2 inhalations twice daily	400/20 microgram
Inhaled high dose corticosteroids	**ZENHALE** 200/5, 2 inhalations twice daily	800/20 microgram

For patients who have not previously received inhaled glucocorticosteroids, but whose disease severity warrants initiation of treatment with two maintenance therapies, depending upon asthma severity, the recommended starting dose is **ZENHALE** 50/5, **ZENHALE** 100/5, or **ZENHALE** 200/5, two inhalations twice daily.

4.2.3 Duration of Treatment

Long-term, twice-daily maintenance treatment for asthma.

4.2.4 Method of Administration

ZENHALE should be administered by oral inhalation only.

4.2.5 Other Important Information

The maximum daily recommended dose is two inhalations of **ZENHALE** 200/5 twice daily for patients 12 years of age and older. If symptoms arise between doses, an inhaled short-acting beta$_2$-agonist should be taken for immediate relief.

Patients should be regularly reassessed by a doctor.

If a previously effective dosage regimen of **ZENHALE** fails to provide adequate control of asthma, the therapeutic regimen should be re-evaluated and additional therapeutic options, e.g., replacing the current strength of **ZENHALE** with a higher strength, adding additional inhaled corticosteroid, or initiating oral corticosteroids, should be considered.

Patients should be made aware that for optimum benefit, **ZENHALE** should be taken regularly, even when they are asymptomatic. Rescue medications only need to be taken to relieve acute asthma symptoms.

If a previously effective dosage regimen of **ZENHALE** fails to provide adequate control of asthma, medical advice should be sought and therapy reassessed, as this may indicate a worsening of the underlying condition.

Missed Dose

If a dose is missed, the patient should be instructed to take the next dose as soon as they remember unless it is near to the time for the next dose, at which time they should wait until the next dose is due. The patient should be instructed not to double the dose.

Geriatrics (≥65 years of age):

Based on available data for **ZENHALE** or its active components, no adjustment of **ZENHALE** in geriatric patients is warranted.

Pediatrics (<12 years of age):

The safety and efficacy of **ZENHALE** have not been established in children less than 12 years of age.

5 COMPANY CORE SAFETY INFORMATION

5.1 Contraindications

Patients with known hypersensitivity to mometasone furoate, formoterol fumarate or to any of the excipients.

5.2 Special Warnings and Special Precautions for Use

General

ZENHALE should not be used to treat acute symptoms of asthma. Adequate education should be provided to the patient regarding the use of long-acting beta$_2$-agonists and the acute treatment of asthma, with close follow up to ensure compliance.

Discontinuance: Treatment with inhaled corticosteroids should not be stopped abruptly in patients with asthma due to risk of exacerbation. In this case, therapy should be titrated down gradually, under physician supervision.

Asthma Exacerbations

In a 26-week, randomized, double-blind, post-marketing clinical trial consisting of 11,729 patients, ages 12 years and older, who received **ZENHALE** or mometasone furoate monotherapy, there were no asthma-related intubations or asthma-related deaths in either treatment arm. **ZENHALE** also significantly reduced the risk of asthma exacerbation as compared to mometasone furoate monotherapy (see section 8 CLINICAL TRIALS for further details).

These results are consistent with three other, similarly designed, post-marketing clinical trials evaluating other ICS/LABA and ICS treatments for asthma, two in 23,360 patients aged 12 years and older (combined n=23,360) and one in 6208 pediatric patients aged 4 to 11 years (n=6208). There were no asthma-related intubations or asthma-deaths in the pediatric trial and none of the 4 studies showed an increased risk of serious asthma events in ICS/LABA compared with ICS. Therefore, these findings are considered applicable to the ICS/LABA class.

ZENHALE should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of asthma. **ZENHALE** has not been studied in patients with acutely deteriorating asthma.

The physician (or health care provider) should reassess asthma therapy if symptoms persist. If after dosing has been increased to maintain control, asthmatic episodes are not responsive to bronchodilators, or the patient exhibits decreased lung function (e.g., peak flow), the underlying condition may have deteriorated. In such cases, consideration should be given to the need for additional corticosteroid or alternative therapies.

Acute Asthma Episodes

ZENHALE is not indicated for rapid relief of bronchospasm or other acute episodes of asthma. In the event of an acute attack, a short-acting beta$_2$-agonist should be used. A short acting beta$_2$-agonist should be available at all times. Patients must be informed of the need to seek medical treatment immediately if their asthma deteriorates suddenly.

Excessive Use of **ZENHALE** and Use with Other Long-Acting Beta$_2$-agonist

ZENHALE should not be used in conjunction with another long-acting beta$_2$-agonist.

The dose of **ZENHALE** should be individualized to the patient's needs and should be at the lowest possible dose to fulfill the therapeutic objective. It should not be increased beyond the maximum recommended dose (see section 4.2 Posology and Method of Administration). No evidence supports that the administration of **ZENHALE** in amounts greater than recommended doses increases efficacy.

Oropharyngeal Candidiasis

During clinical trials with **ZENHALE**, oral candidiasis, which is associated with the use of inhaled glucocorticosteroids, occurred in some patients. This infection may require treatment with appropriate antifungal therapy and in some patients discontinuance of **ZENHALE** may be necessary. After dosing with **ZENHALE**, advise patients to rinse their mouth with water and spit out the contents without swallowing.

Immunosuppression

Use **ZENHALE** with caution, if at all, in patients with active or quiescent tuberculous infections of the respiratory tract, or in untreated fungal, bacterial, systemic viral infections or ocular herpes simplex.

Advise patients who are receiving corticosteroids or other immunosuppressant medicines of the risk of exposure to certain infections (e.g., chickenpox, measles) and of the importance of obtaining medical advice if such exposure occurs. This is of particular importance in children. If exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with pooled intravenous immunoglobulin (IG) may be indicated. If chickenpox develops, treatment with antiviral agents may be considered.

Immediate hypersensitivity, reactions including angioedema, urticaria, flushing and bronchospasm may occur after administration of **ZENHALE**.

Transferring from Systemic Corticosteroid Therapy

Particular care is needed for patients who are transferred from systemically active corticosteroids to **ZENHALE**, because deaths due to adrenal insufficiency have occurred in asthmatic patients during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids. After withdrawal from systemic corticosteroids, a number of months are required for recovery of hypothalamic-pituitary-adrenal (HPA) axis function.

During periods of stress, including trauma, surgery, or infection, or a severe asthma attack, patients transferred from systemic corticosteroids will require supplementary treatment with a short course of systemic corticosteroids, which is gradually tapered as symptoms subside. It is recommended that such patients carry a supply of oral corticosteroids and a warning card indicating their need and recommended dosage of systemic corticosteroids during stressful periods. Periodic testing of adrenocortical function, particularly measurement of early morning plasma cortisol levels, is recommended.

Transfer of patients from systemic corticosteroid therapy to **ZENHALE** may unmask pre-existing allergic conditions previously suppressed by systemic corticosteroid therapy. If this occurs, symptomatic treatment is recommended.

Systemic Effects of Corticosteroids

Systemic effects of inhaled corticosteroids may occur, particularly at high doses prescribed for prolonged periods. These effects are much less likely to occur than with oral corticosteroids. Possible systemic effects include adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataracts and glaucoma. Therefore, it is important that the dose of **ZENHALE** is titrated to the lowest dose at which effective control of asthma is maintained.

Rare cases of cataracts and glaucoma have been reported with use of mometasone furoate.

Visual disturbance may be reported with systemic and topical (including, intranasal, inhaled and intraocular) corticosteroid use. If a patient presents with symptoms such as blurred vision or other visual disturbances, the patient should be considered for referral to an ophthalmologist for evaluation of possible causes of visual disturbances which may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids.

Adrenal Suppression

ZENHALE will usually permit control of asthma symptoms with less suppression of HPA axis function than therapeutically equivalent oral doses of prednisone.

When using inhaled corticosteroids, the possibility for clinically significant adrenal suppression may occur, especially after treatment with higher than recommended doses. This must be considered during periods of stress or elective surgery, when additional systemic corticosteroids may be needed. However, during clinical trials the effects of **ZENHALE** (at doses of mometasone furoate 800 mcg/day) on plasma cortisol were not clinically significant.

Inhalation Induced Bronchospasm

As with other inhalation therapy, the potential for inhalation induced bronchospasm should be kept in mind. If it occurs, the preparation should be discontinued immediately and alternative therapy substituted.

Cardiovascular & Concomitant Conditions

ZENHALE, like other beta$_2$-agonist containing product, should be used with caution in patients with ischemic heart disease, cardiac arrhythmias (especially third-degree atrioventricular block), severe cardiac decompensation, idiopathic subvalvular aortic stenosis, severe hypertension, aneurysm, pheochromocytoma, hypertrophic obstructive cardiomyopathy, thyrotoxicosis, known or suspected

prolongation of the QT interval (QTc >0.44 sec; see section 5.3 Interactions with Other Medicinal Products and Other Forms of Interaction).

Hypokalemia and Hyperglycemia

Potentially serious hypokalemia may occur as a result of beta$_2$-agonist therapy. Hypokalemia may increase susceptibility to cardiac arrhythmias.

Particular caution is advised in patients with severe asthma as hypokalemia may be potentiated by hypoxia and concomitant treatment (see section 5.3 Interactions with Other Medicinal Products and Other Forms of Interaction). It is recommended that serum potassium levels be monitored in such situations.

Due to the hyperglycemic effect of beta$_2$-stimulants, including formoterol, additional blood glucose monitoring is recommended in diabetic patients.

There is an enhanced effect of corticosteroids on patients with hypothyroidism.

Hepatic/Biliary/Pancreatic

There is an enhanced effect of corticosteroids on patients with cirrhosis.

5.3 Interactions with Other Medicinal Products and Other Forms of Interaction

In clinical studies, concurrent administration of **ZENHALE** and other drugs, such as short-acting beta$_2$-agonist and intranasal corticosteroids have not resulted in an increased frequency of adverse drug reactions. No formal drug interaction studies have been performed with **ZENHALE.** The drug interactions of the combination are expected to reflect those of the individual components.

Interactions with strong CYP3A4 inhibitors:

Co-administration with strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, ritonavir, cobicistat-containing products) may lead to increased plasma concentrations of corticosteroids and potentially increase the risk for systemic corticosteroid side-effects. Consider the benefit of co-administration versus the potential risk of systemic corticosteroid effects, in which case patients should be monitored for systemic corticosteroid side-effects.

Adrenergic agents:

Concomitant administration of other sympathomimetic agents may potentiate the undesirable effects of formoterol.

Xanthine derivatives and diuretics:

Concomitant treatment with xanthine derivatives, or non-potassium sparing diuretics may potentiate the possible hypokalaemic effect of beta$_2$-agonists (see section 5.2 Special Warnings and Special Precautions for Use).

Monoamine oxidase inhibitors, tricyclic antidepressants, and drugs known to prolong the QTc interval:

Formoterol, as other beta$_2$-agonists, should be administered with caution to patients being treated with drugs such as quinidine, disopyramide, procainamide, phenothiazines, terfenadine, astemizole, macrolides, monoamine oxidase inhibitors and tricyclic antidepressants or any drug known to prolong the QTc interval, because the action of adrenergic agonists on the cardiovascular system may be potentiated by these agents. Drugs that are known to prolong the QTc-interval have an increased risk of ventricular arrhythmia (see section 5.2 Special Warnings and Special Precautions for Use).

Beta-adrenergic receptor antagonists:

Beta-adrenergic blockers may weaken or antagonise the effect of formoterol. Therefore formoterol should not be given together with beta-adrenergic blockers (including eye drops) unless there are compelling reasons for their use.

Halogenated Hydrocarbons:

There is an elevated risk of arrhythmias in patients receiving concomitant anesthesia with halogenated hydrocarbons.

5.4 Pregnancy and Lactation

Pregnancy

There are no adequate and well-controlled studies of **ZENHALE** use in pregnant women. Studies in animals with mometasone furoate, like other glucocorticoids, have shown reproductive toxicity; however, the potential risk for humans is unknown. **ZENHALE** should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus.

Infants born of mothers who received corticosteroids during pregnancy are to be observed carefully for hypoadrenalism.

Like other beta$_2$-adrenergic stimulants, formoterol may inhibit labour due to a relaxant effect on uterine smooth muscle.

Lactation

There are no data from well-controlled human studies on the use of **ZENHALE** on nursing mothers. Formoterol has been detected in the milk of lactating rats and other corticosteroids are excreted in human milk. Based on data for the individual components, a decision on whether to continue/discontinue therapy with **ZENHALE** should be made taking into account the benefit of breast-feeding to the child and the benefit of **ZENHALE** therapy to the women.

5.5 Specific Populations

5.5.1 Pediatric Population <12 years of age:

The safety and efficacy of **ZENHALE** have not been established in children less than 12 years of age.

5.5.2 Adolescent Population 12 to 17 years of age:

The safety and efficacy of **ZENHALE** have been established in 151 patients 12 to 17 years of age across 5 clinical trials up to 52 weeks in duration. Patients in this age-group demonstrated efficacy and safety results similar to those observed in patients 18 years of age and older. In addition, in a 26-week post-marketing trial consisting of 5868 patients treated with **ZENHALE**, similar safety and efficacy results were observed in 491 adolescent patients (ages 12 to 17 years) compared to 4578 adult (18 to ≤64 years of age) and 799 geriatric (≥65 years of age) patients who were treated with **ZENHALE**.

5.5.3 Geriatric Population ≥65 years of age:

The safety and efficacy of **ZENHALE** have been established in 118 patients 65 years of age and older across 5 clinical trials up to 52 weeks in duration. Patients in this age-group demonstrated efficacy and safety results similar to those observed in patients 18 years of age and older. In addition, in a 26-week post-marketing trial consisting of 5868 patients treated with **ZENHALE**, similar safety and efficacy results were observed in 799 geriatric (≥65 years of age) patients compared to 4578 adult (18 to ≤64 years of age) and 491 adolescent (ages 12 to 17 years) patients who were treated with **ZENHALE**.

5.6 Undesirable Effects

5.6.1 Overview

ZENHALE contains both mometasone furoate and formoterol, therefore the type and severity of adverse reactions associated with each individual component of **ZENHALE** may be expected. There is no evidence of additional adverse events following concurrent administration of the two components.

Tremor, palpitations, electrocardiogram QT prolongation, tachycardia, hypertension and headache have been reported and are associated with pharmacological side effects of beta$_2$-agonist treatment (including **ZENHALE**). Cardiac arrhythmias (including atrial fibrillation, supraventricular tachycardia and ventricular extrasystoles) may occur in some patients.

Rarely, hypersensitivity reactions, including rash, urticaria, bronchospasm, arthralgia, angioedema, and anaphylactic reaction may occur in some patients.

Due to the mometasone furoate component for oral inhalation, oral candidiasis can occur in some patients. Incidence of oral candidiasis may be reduced by rinsing the mouth with water after using the product. Symptomatic candidiasis can be treated with topical antifungal therapy.

Systemic and local corticosteroid use may also result in the following:

- Immunosuppression
- Hypercorticism and adrenal suppression
- Growth retardation in children
- Glaucoma and cataracts
- Reduced bone density, osteoporosis and fracture

As with other inhalation therapy, inhalation induced bronchospasm may occur rarely.

See “Special Warnings and Special Precautions for Use” for more detailed information.

5.6.2 Clinical Trials Experience

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Safety data is based on the 3 pivotal clinical trials (P04073, P04334, and P04431) and the long term safety trial (P04139). The total number of patients (12 years of age and older with asthma) participating in these studies was 2659, of which 1131 were exposed to **ZENHALE.** Eight hundred and sixty (860) patients were exposed to **ZENHALE** in the 12 to 26-week studies and 271 patients were exposed to **ZENHALE** in the 1 year study.

Table 2 demonstrates the incidence of treatment related adverse reactions associated with **ZENHALE** based upon the pooled data of the three pivotal clinical trials.

Table 2: Treatment related adverse reactions in ZENHALE groups occurring at an incidence of ≥1% and

more commonly than placebo								
Adverse Reaction	ZENHALE*			Mometasone Furoate*			Formoterol*	Placebo*
	50/5 n=182 n (%)	100/5 n=424 n (%)	200/5 n=255 n (%)	50 mcg n=188 n (%)	100 mcg n=192 n (%)	200 mcg n=240 n (%)	5 mcg n=390 n (%)	n=384 n (%)
Oral Candidiasis	3 (1.6)	4 (0.9)	4 (1.6)	1 (0.5)	1 (0.5)	2 (0.8)	3 (0.8)	3 (0.8)
Nausea	2 (1.1)	0	0	0	0	0	0	0
Headache	2 (1.1)	1 (0.2)	1 (0.4)	1 (0.5)	1 (0.5)	0	2 (0.5)	2 (0.5)
Pharyngolaryngeal pain	2 (1.1)	0	0	1 (0.5)	0	0	3 (0.8)	0
Average Duration of Exposure (days)	162	116	81	159	165	79	139	137

These results are based on clinical trials P04073, P04334 & P04431.

*All treatments were administered as two inhalations twice daily.

In a comparator safety study of one year treatment duration, patients 12 years of age and older were treated with medium dose **ZENHALE** 100/5 (n=141), high dose **ZENHALE** 200/5 (n=130) or an active comparator (n=133, 68 medium dose and 65 high dose inhaled corticosteroid/LABA combination).

Safety outcomes were similar to those observed in the 12 to 26-week trials and no treatment related deaths or clinically judged asthma deteriorations or reduction in lung function were observed.

Dysphonia was observed at a higher frequency in the longer term treatment trial at a reported incidence of 7/141 (5%) patients receiving **ZENHALE** 100/5 and 4/130 (3.1%) patients receiving **ZENHALE** 200/5. Overall, through 52 weeks of observation, 15 patients demonstrated a ≥1.0 point change in LOCS III score (measured at the Week 26 and Week 52 timepoints using the Lens Opacities Classification System, Version III) from Baseline. At Week 26, in the medium dose group, 2 (1.4%) patients receiving **ZENHALE** 100/5 and 4 (5.9%) patients receiving an active comparator demonstrated ocular changes. In the high dose group, 3 (2.3%) patients receiving **ZENHALE** 200/5 demonstrated ocular changes (no patients in the active comparator group). At Week 52, in the medium dose group, 4 (2.8%) patients receiving **ZENHALE** 100/5 and 1 (1.5%) patient receiving an active comparator demonstrated ocular changes. In the high dose group 3 (2.3%) patients receiving **ZENHALE** 200/5 and 1 (1.5%) patient receiving an active comparator demonstrated ocular changes. No incidences of appearance of posterior subcapsular cataracts typically associated with chronic use of high dose inhaled corticosteroid were reported in this clinical study. No clinically significant changes in blood chemistry, hematology, or ECG were observed.

Less Common Clinical Trial Adverse Drug Reactions (<1%)

The following additional treatment related adverse reactions occurred in these clinical trials (P04073, P04334, P04431, P04139) in patients using **ZENHALE** with an incidence of <1% and occurred at a greater incidence than placebo:

Cardiac Disorders: tachycardia, palpitations
Gastrointestinal Disorders: dry mouth
Immune System Disorders: hypersensitivity reactions with the following manifestations – bronchospasm, dermatitis allergic, urticaria
Infections and Infestations: pharyngitis
Musculoskeletal and Connective Tissue Disorders: muscle spasms*
Nervous System Disorders: tremor, dizziness*
Psychiatric Disorders: insomnia, nervousness*
Respiratory, Thoracic and Mediastinal Disorders: throat irritation
Vascular disorders: hypertension

*Reported in the 52-week safety study (P04139)

Electrocardiogram QT prolongation occurred at the same incidence as placebo (<1%).

In a 26-week, randomized, double-blind, post-marketing clinical trial consisting of 11,729 patients, ages 12 years and older, who received at least one dose of **ZENHALE** (100 mcg/5 mcg or 200 mcg/5 mcg) or mometasone furoate monotherapy (100 mcg or 200 mcg), safety outcomes were generally comparable to those observed in earlier clinical trials; no new safety signals were identified. All-cause hospitalizations, intubations, and deaths were balanced between the treatment arms (Table 3). There were no asthma-related intubations (endotracheal) or asthma-related deaths in either treatment arm (see section 8 CLINICAL TRIALS, Table 6). The overall incidence of serious adverse events was low (2.3%) and balanced between the treatment arms. All serious adverse event terms in both treatment arms were <1%. Treatment discontinuations due to adverse events or due to asthma exacerbation were low and balanced between the treatment groups, occurring in 186 (1.6%), and 155 (1.3%) of the patients, respectively.

Table 3. Summary of Safety Events Occurring in ZENHALE Relative to Mometasone Furoate Monotherapy

Safety Events	ZENHALE n=5868	Mometasone furoate n=5861	Overall n=11,729

All-cause hospitalization	143	147	290
All-cause intubation	24	32	56
All-cause death	5	4	9

5.6.3 Post-Market Experience

The following additional adverse reactions have been reported in post-marketing use with **ZENHALE** or post-marketing use with inhaled mometasone furoate or inhaled formoterol fumarate: hypokalaemia; hyperglycaemia; angina pectoris; cardiac arrhythmias (e.g., atrial fibrillation, ventricular extrasystoles, tachyarrhythmia); hypersensitivity reactions (e.g., rash, angioedema and anaphylactic reaction); asthma aggravation (e.g., cough, dyspnea, wheezing and bronchospasm); and vision blurred.

5.7 Overdosage

ZENHALE contains both mometasone furoate and formoterol fumarate; therefore, the risks associated with overdosage for the individual components described below apply to **ZENHALE**.

Symptoms:

Mometasone furoate

Inhalation or oral administration of excessive doses of corticosteroids may lead to suppression of HPA axis function.

Formoterol fumarate

Excessive formoterol fumarate is likely to lead to effects that are typical of beta$_2$-adrenergic stimulants: nausea, vomiting, headache, tremor, drowsiness, palpitations, tachycardia, ventricular arrhythmias, metabolic acidosis, hypokalaemia, hyperglycaemia, hypertension.

Treatment:

Supportive and symptomatic treatment is indicated. In serious cases, patients should be hospitalised. Use of cardioselective beta-blockers may be considered, but only under the supervision of a physician and with extreme caution since the use of beta-adrenergic blocker medication may provoke bronchospasm. Adrenal function monitoring should be included as part of management.

6 PHARMACOLOGICAL PROPERTIES

6.1 Pharmacodynamic Properties

6.1.1 Pharmacotherapeutic Group

Mometasone furoate is a topical glucocorticosteroid with local anti-inflammatory properties and formoterol is a potent selective beta$_2$-adrenergic stimulant.

6.1.2 Mechanism of Action

ZENHALE contains both mometasone furoate and formoterol fumarate; therefore, the mechanisms of actions described below for the individual components apply to **ZENHALE**.

Mometasone furoate

Mometasone furoate is a topical glucocorticosteroid with local anti-inflammatory properties.

Glucocorticoids, like mometasone furoate exert their anti-inflammatory effects through glucocorticoid receptors (GRs). On binding the glucocorticoid, the GR heterocomplex dissociates, and the ligand activated GR translocates from the cytoplasm to the nucleus. The activated GR may then upregulate the transcription of anti-inflammatory genes by binding to specific DNA sequences termed glucocorticoid response elements. However, it is more likely that it is the ability of glucocorticoids to suppress the transcription of genes may be their primary activity to suppress inflammation. In this case, the activated GR interacts with transcription factors apolipoprotein 1 (AP 1) or nuclear factor kappa B (NF-kB) to down regulate gene expression. In addition, glucocorticoids have been shown to upregulate the expression of an inhibitor of NF-kB.

Formoterol fumarate

Formoterol is a potent selective beta$_2$-adrenergic stimulant. It exerts a bronchodilator effect in patients with reversible airways obstruction lasting for 12 hours. Formoterol inhibits the release of histamine and leukotrienes from passively sensitised human lung. Some anti-inflammatory properties, such as inhibition of oedema and inflammatory cell accumulation, have been observed in animal experiments.

6.1.3 Pharmacodynamic Effects

Mometasone furoate

Affinity for binding to the GR corresponds to functional activity. Mometasone furoate binds with very high affinity to the human GR and this leads to its potent inhibitory effects on cells to reduce the synthesis and release of proinflammatory mediators and cytokines.

Mometasone furoate significantly inhibits the release of leukotrienes from leucocytes of allergic patients. In cell culture, mometasone furoate demonstrated high potency in inhibition of synthesis and release of IL-1, IL-5, IL-6, and TNFα; it is also a potent inhibitor of the production of the TH2 cytokines, IL-4 and IL-5, from human CD4+ T-cells. In mixed leukocytes from atopic patients, mometasone furoate was a more potent inhibitor of leukotriene production than BDP.

In preclinical models, mometasone furoate has been shown to reduce the accumulation of inflammatory cells, including eosinophils, infiltrating into the upper and lower airways and improve lung function following allergen provocation. Additionally, mometasone furoate reduced the number of lymphocytes and the levels of messenger RNA for the proallergic cytokines IL-4 and IL-5.

Formoterol fumarate

In vitro studies on guinea pig trachea have indicated that racemic formoterol and its (R,R)- and (S,S)-enantiomers are highly selective beta$_2$-adrenoceptor agonists. The (S,S)-enantiomer was 800 to 1,000 times less potent than the (R,R)-enantiomer and did not affect the activity of the (R,R)-enantiomer on tracheal smooth muscle. No pharmacological basis for the use of one of the two enantiomers in preference to the racemic mixture was demonstrated.

Clinical Safety

In patients 12 years of age and older with asthma, there was no evidence of significant hypokalemia or hyperglycemia in response to formoterol treatment after doses of formoterol fumarate ranging from 10 microgram to 40 microgram from **ZENHALE**. No relevant changes in heart rate and blood pressure were observed during studies with **ZENHALE** and the effects were comparable to that of the individual components. No patients had a QTcB (QTc corrected by Bazett's formula) ≥500 msec during treatment. There were no other clinically significant abnormalities, including vital signs, or ECG data.

The effects of inhaled mometasone furoate administered via **ZENHALE** on adrenal function were evaluated in two clinical studies in patients with asthma. HPA-axis function was assessed by 24-hour plasma cortisol AUC. Dose related decreases in plasma cortisol were observed with **ZENHALE** but these effects are not considered to be clinically significant.

6.2 Pharmacokinetic Properties

6.2.1 General Introduction

In a single-dose crossover study, there was no evidence of a pharmacokinetic interaction between mometasone furoate and formoterol when given as **ZENHALE**.

6.2.2 Absorption and Bioavailability

Mometasone furoate

Following inhalation of single and multiple doses of the **ZENHALE**, mometasone furoate (200 to 800 microgram) was rapidly absorbed with a prolonged absorption phase. Median T_{max} values ranged from 0.50 to 4 hours. Exposure to mometasone furoate increased with increasing inhaled dose. Absorbed mometasone furoate is rapidly cleared from plasma at a rate of approximately 12.5 mL/min/kg, independent of dose. The effective $t_{½}$ for mometasone furoate following inhalation with **ZENHALE** was 25 hours. Using the steady-state exposure to mometasone furoate when administered by inhalation from **ZENHALE** and after a single IV dose from different studies, estimates of the absolute bioavailability were approximately 14% in healthy subjects and ranged from 5% to 7% in asthmatic patients.

Formoterol fumarate

Following **ZENHALE** administration formoterol was rapidly absorbed with median T_{max} values ranging from 0.17 to 1.97 hours. Over the dose range of 10 to 40 microgram for formoterol from **ZENHALE**, the exposure to formoterol was dose proportional. The mean $t_{½}$ for formoterol in plasma were 9.1 hours.

6.2.3 Distribution

Mometasone furoate

After intravenous bolus administration, the mean steady-state volume of distribution (V_d) is 152 L. The *in vitro* protein binding for mometasone furoate is high, 98% to 99% in concentration range of 5 to 500 ng/ml.

Formoterol fumarate

The plasma protein binding of formoterol was 61 to 64%, and binding to human serum albumin was 34%.

6.2.4 Metabolism

Mometasone furoate

Mometasone furoate is extensively metabolized in all species investigated. No major metabolites have been identified. The portion of an inhaled mometasone furoate dose that is swallowed and absorbed from the gastrointestinal tract undergoes extensive metabolism to multiple metabolites. In human liver

microsomes, mometasone furoate is metabolized to many metabolites, including 6-beta hydroxy mometasone furoate, which is formed by cytochrome P_{450}3A4.

Formoterol fumarate

Formoterol is eliminated primarily by metabolism, with direct glucuronidation being the major pathway of biotransformation. O-demethylation followed by glucuronidation is another pathway. Minor pathways involve sulphate conjugation of formoterol and deformylation followed by sulphate conjugation. Multiple isozymes catalyse the glucuronidation (UGT1A1, 1A3, 1A6, 1A7, 1A8, 1A9, 1A10, 2B7 and 2B15) and O-demethylation (CYP2D6, 2C19, 2C9 and 2A6) of formoterol, suggesting a low potential for drug-drug interactions though inhibition of a specific isozyme involved in formoterol metabolism. Formoterol did not inhibit cytochrome P450 isozymes at therapeutically relevant concentrations.

6.2.5 Elimination

Mometasone furoate

A radiolabeled, orally inhaled dose is excreted mainly in the feces (74%) and to a lesser extent in the urine (8%).

Formoterol fumarate

Following oral administration of 80 microgram of radiolabeled formoterol fumarate to 2 healthy subjects, 59% to 62% of the radioactivity was eliminated in the urine and 32% to 34% in the feces over a period of 104 hours. In an oral inhalation study with **ZENHALE**, renal clearance of formoterol from the blood was 217 mL/min. Following single inhaled doses of formoterol ranging from 10 to 40 microgram from **ZENHALE**, 6.2% to 6.8% of the formoterol dose was excreted in urine unchanged.

6.3 Special Populations and Conditions

Paediatrics: The pharmacokinetics of **ZENHALE** has not been specifically studied in children below 12 years of age.

Geriatrics: The pharmacokinetics of **ZENHALE** has not been specifically studied in the elderly population.

Gender: Studies to examine the effects of gender on the pharmacokinetics of **ZENHALE** have not been specifically conducted. Based on analysis of single and multiple dose pharmacokinetics studies, no effect of gender on mometasone furoate and formoterol exposure was observed.

Race: Studies to examine the effects of race on the pharmacokinetics of **ZENHALE** have not been specifically conducted.

Hepatic Insufficiency: The pharmacokinetics of **ZENHALE** has not been specifically studied in patients with hepatic impairment. Concentrations of mometasone furoate appear to increase with severity of hepatic impairment. These increases are not considered to be clinically significant. A study evaluating the administration of a single inhaled dose of 400 mcg mometasone furoate by a dry powder inhaler to subjects with mild (n=4), moderate (n=4), and severe (n=4) hepatic impairment resulted in only 1 or 2 subjects in each group having detectable peak plasma concentrations of mometasone furoate (ranging from 50-105 pg/mL). The observed peak plasma concentrations appear to increase with severity of hepatic impairment; however, the numbers of detectable levels were few.

Renal Insufficiency: The pharmacokinetics of **ZENHALE** has not been specifically studied in patients with renal impairment.

7 NONCLINICAL TOXICOLOGY

ZENHALE contains both mometasone furoate and formoterol fumarate; therefore, the mutagenesis, carcinogenesis, impairment of fertility, and reproduction toxicity information of the individual components described below apply to **ZENHALE**.

The toxicity observed in animal studies with mometasone furoate and formoterol fumarate, given in combination as **ZENHALE** or separately, were effects associated with exaggerated pharmacological activity.

In 2- and 13-week inhalation toxicity studies conducted in rats and dogs using formulations containing ratios of 50:5 and 200:5 mometasone furoate:formoterol fumarate dihydrate, all findings were consistent with toxicities that would be expected with the individual active drugs. No new or additive toxicities were observed. No pharmacokinetic interactions were observed after coadministration of mometasone furoate and formoterol fumarate.

7.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Mutagenesis

Mometasone furoate

Mometasone furoate was non-mutagenic in the mouse-lymphoma assay and the Salmonella/*E. coli* mammalian microsome mutagenicity bioassay. At cytotoxic doses only, mometasone furoate produced an increase in chromosome aberrations *in vitro* in Chinese hamster ovary cell (CHO) cultures

in the non-activation phase, but not in the presence of rat liver S9 fraction. However, mometasone furoate did not induce chromosomal aberrations *in vitro* in a Chinese hamster lung cell (CHL) chromosomal-aberrations assay, or *in vivo* in the mouse bone marrow erythrocyte-micronucleus assay, in the rat bone-marrow clastogenicity assay, and the mouse male germ-cell clastogenicity assay. Mometasone furoate also did not induce unscheduled DNA synthesis *in vivo* in rat hepatocytes. The finding of simple chromosomal aberrations in the non-activation phase of the CHO assay is considered to be related to cytotoxicity and is not considered to be of significance in the risk assessment of mometasone furoate because of the negative results in the S9 phase of this assay, the negative results in a second *in vitro* chromal aberrations assay (CHL assay), and the negative results in three *in vivo* chromosomal aberrations assays.

Formoterol fumarate

Mutagenicity tests covering a broad range of experimental endpoints have been conducted. No genotoxic effects were found in any of the *in vitro* or *in vivo* tests performed.

Carcinogenesis

Mometasone furoate

In a 2-year carcinogenicity study in Sprague Dawley rats, mometasone furoate demonstrated no statistically significant increase in the incidence of tumours at inhalation doses up to 67 mcg/kg (approximately 8 times the maximum recommended daily inhalation dose in adults on an AUC basis and 2 times the maximum recommended daily inhalation dose in pediatric patients based on a mcg/m^2 bases). In a 19-month carcinogenicity study in Swiss CD-1 mice, mometasone furoate demonstrated no statistically significant increase in the incidence of tumours at inhalation doses up to 160 mcg/kg (approximately 10 times the maximum recommended daily inhalation dose in adults on an AUC basis and 2 times the maximum recommended daily inhalation dose in pediatrics patients base on a mcg/m^2 bases).

Formoterol fumarate

Two-year studies in rats and mice did not show any carcinogenic potential.

Male mice treated at very high dose levels showed a slightly higher incidence of benign adrenal subcapsular cell tumours. However, this finding was not seen in a second mouse feeding study, in which pathological changes at high doses consisted of an increased incidence both of benign smooth muscle tumours in the female genital tract, and of liver tumours in both sexes. Smooth muscle tumours are a known effect of beta-agonists given at high doses in rodents.

Two studies in rats, covering different dose ranges, showed an increase in mesovarial leiomyomas. These benign neoplasms are typically associated with long-term treatment of rats at high doses of $beta_2$-

adrenergic drugs. Increased incidences of ovarian cysts and benign granulosa/thecal cell tumours were also seen; beta-agonists are known to have effects on the ovary in rats which are very likely specific to rodents. A few other tumour types noted in the first study using the higher doses were within the incidences of the historical control population, and were not seen in the lower-dose experiment.

None of the tumour incidences were increased to a statistically significant extent at the lowest dose of the second rat study, a dose leading to a systemic exposure 10 times higher than that expected from the maximum recommended dose of formoterol in humans.

On the basis of these findings and the absence of a mutagenic potential, it is concluded that use of mometasone furoate and formoterol at therapeutic doses does not present a carcinogenic risk.

Impairment of Fertility

Mometasone furoate

In studies of reproductive function, subcutaneous mometasone furoate was well tolerated at doses up to 7.5 µg/kg. At 15 µg/kg, mometasone furoate caused prolonged gestation and prolonged and difficult labor occurred with a reduction in offspring survival and body weight or body weight gain. There was no effect on fertility.

Formoterol fumarate

Reproduction studies in rats revealed no impairment of fertility at oral doses up to 3 mg/kg (approximately 1000 times the maximum recommended daily inhalation dose in humans on a mg/m^2 basis).

7.2 Teratogenicity

Mometasone furoate

Like other glucocorticoids, mometasone furoate is a teratogen in rodents and rabbits. Teratology studies were conducted in rats, mice and rabbits by the oral, topical and/or subcutaneous routes. Effects noted were umbilical hernia in rats, cleft palate in mice, and gall bladder agenesis, umbilical hernia, and flexed front paws in rabbits. There were also reductions in maternal body weight gains, effects on fetal growth (lower fetal body weight and/or delayed ossification) in rats, rabbits and mice, and reduced offspring survival in mice.

In an oral teratology study in rabbits, at 700 µg/kg, increased incidences of resorption and malformations, including cleft palate and/or head malformations (hydrocephaly or domed head) were observed. Pregnancy failure was observed in most rabbits at 2800 µg/kg.

7.3 Other Effects

Preclinical studies demonstrate that mometasone furoate is devoid of androgenic, anti-androgenic, estrogenic or anti-estrogenic activity but, like other glucocorticoids, it exhibits some anti-uterotrophic activity and delays vaginal opening in animal models at high oral doses of 56 mg/kg/day and 280 mg/kg/day.

8 CLINICAL TRIALS

The safety and efficacy of **ZENHALE** were demonstrated in three randomized, double-blind, parallel group, multicentered clinical studies of 12 to 26 weeks in duration involving 2,255 patients 12 years of age and older. Patients with persistent asthma uncontrolled on low, medium or high dose inhaled corticosteroids (baseline FEV_1 means of 66% to 75% of predicted normal) were enrolled in **ZENHALE** 50/5, **ZENHALE** 100/5, or **ZENHALE** 200/5 studies, respectively. All of the studies included a 2 to 3-week run-in period with mometasone furoate to establish a level of asthma control consistent with current medical practice. **ZENHALE** was evaluated in two-double blind placebo controlled studies which also included its individual components, mometasone furoate and formoterol fumarate and 1 clinical study evaluated two different strengths of **ZENHALE** compared with mometasone furoate alone. Superior efficacy was established with **ZENHALE** in all primary and key secondary endpoints measuring lung function, asthma symptoms and quality of life.

The safety and efficacy of **ZENHALE** are further supported by results from a 26-week post-marketing, randomized, double-blind, active-comparator, global study of **ZENHALE** (100 mcg/5 mcg or 200 mcg/5 mcg) versus mometasone furoate metered dose inhalation (MDI) monotherapy (100 mcg or 200 mcg) patients, 12 years of age and older. Unlike earlier trials, there was no run-in period; at randomization patients had been receiving a stable dose of inhaled corticosteroid or other asthma maintenance therapies for at least 4 weeks, and had a disease severity that warranted treatment with ICS ± LABA.

ZENHALE 50/5 and 100/5 Studies

In the two 26-week studies, patients who received **ZENHALE** 50/5 or 100/5 had statistically significant greater improvement in lung function as measured by serial FEV_1 compared with mometasone furoate and versus placebo.

Patients who received **ZENHALE** 50/5 or 100/5 are less likely to experience an asthma exacerbation or asthma attack as compared with patients who received formoterol fumarate and placebo, see Table 4.

Table 4. Asthma Exacerbations and Asthma Attacks

	ZENHALE 50/5 Study				ZENHALE 100/5 Study			
	ZENHALE 50/5	Placebo	Mometasone furoate 50 µg	Formoterol fumarate 5 µg	ZENHALE 100/5	Placebo	Mometasone furoate 100 µg	Formoterol fumarate 5 µg
Patients with severe asthma exacerbations*	30 (16.5%)	86 (45.7%)	53 (28.2%)	84 (44.7%)	58 (30.4%)	109 (55.6%)	65 (33.9%)	109 (54.0%)
Patients with mild asthma exacerbations†	61 (33.5%)	123 (65.4%)	91 (48.4%)	104 (55.3%)	88 (46.1%)	139 (70.9%)	96 (50.0%)	136 (67.3%)
Patients with clinical deterioration (asthma attack)‡	3 (1.6%)	27 (14.4%)	5 (2.7%)	17 (9.0%)	5 (2.6%)	33 (16.8%)	10 (5.2%)	31 (15.3%)

* A severe asthma exacerbation was defined as 1 of the following: a 20% decrease in FEV_1; a 30% decrease in PEF on two consecutive days; an occurrence of an asthma attack characterized as a clinical deterioration of asthma that results in emergency treatment, hospitalization, or treatment with systemic corticosteroids.

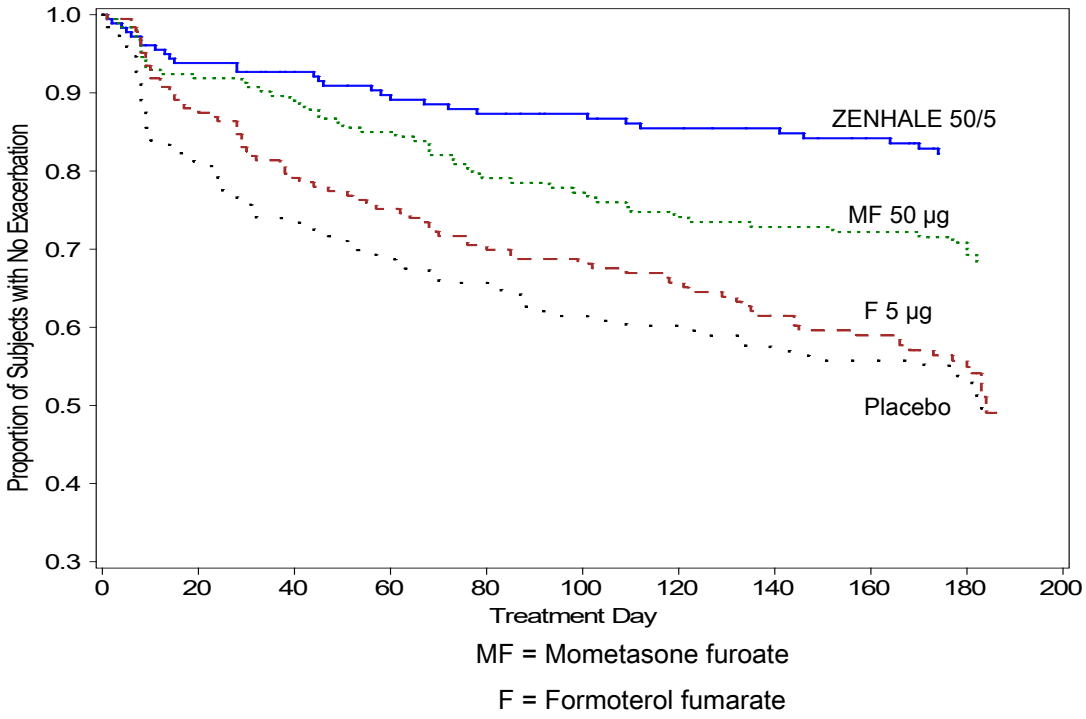
† A mild asthma exacerbation was defined as an occurrence of any 1 of the three following criteria: two consecutive nights with 1 or more nocturnal awakenings due to asthma symptoms requiring SABA rescue medication; a decrease in AM or PM PEF of 25% on 2 consecutive days of treatment; or more than 8 combined units of SABA rescue medication use on 2 consecutive days.

‡ A clinical deterioration of asthma (asthma attack) was defined as unscheduled visit requiring emergency treatment, hospitalization due to asthma, or treatment with additional asthma medication including systemic corticosteroids.

ZENHALE 50/5 and 100/5 delayed time to first severe exacerbations as compared with patients who received formoterol fumarate and placebo as shown in Figure 1 and 2.

Figure 1 – ZENHALE 50/5 Study: Time to First Severe Asthma Exacerbation

Kaplan-Meier Survival Curve

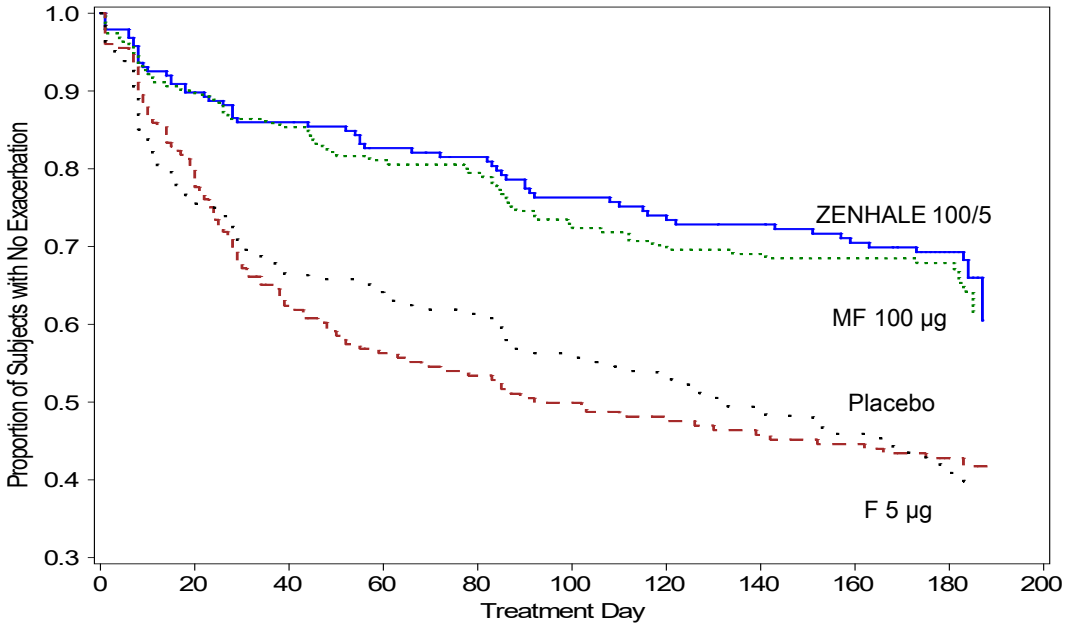


MF = Mometasone furoate

F = Formoterol fumarate

Figure 2 – ZENHALE 100/5 Study: Time to First Severe Asthma Exacerbation

Kaplan-Meier Survival Curve



MF = Mometasone furoate

F = Formoterol fumarate

Clinically meaningful improvement in asthma specific quality of life (as measured by Asthma Quality of Life Questionnaire [AQLQ(S) 12+]) and asthma control (as measured by Asthma Control Questionnaire

[ACQ]) was observed in patients receiving **ZENHALE** 50/5 or 100/5 as compared with patients receiving placebo. At study endpoint, patients receiving **ZENHALE** 50/5 or 100/5 were more likely to have well-controlled asthma compared with patients receiving placebo.

Patients who received **ZENHALE** 50/5 and 100/5 had improved asthma symptom scores and a decreased proportion of nights with nocturnal awakenings as compared with patients receiving formoterol fumarate and versus placebo. Patients who received **ZENHALE** 50/5 and 100/5 had a decreased short-acting beta$_2$-agonist use as compared to patients receiving placebo and improved pre-dose morning PEF as compared to all treatment arms.

ZENHALE 200/5 Study

In a 12-week study in patients with persistent asthma and prior asthma exacerbations, **ZENHALE** 100/5 and **ZENHALE** 200/5 had a greater improvement in FEV_1 compared with mometasone furoate 200 microgram. Patients receiving **ZENHALE** 200/5 had a greater numerical increase in serial FEV_1 from baseline as compared with patients receiving **ZENHALE** 100/5 across the 12-week treatment period.

In a sub-group analysis, patients with a lower baseline percent predicted FEV_1 below the overall median who received **ZENHALE** 200/5 had greater increase in FEV_1 as compared with patients who received **ZENHALE** 100/5 at Week 12.

There were no signs of reduction in the 12-hour bronchodilator effect with either **ZENHALE** 50/5, 100/5, or 200/5 after 12 or 26 weeks of therapy.

Post-marketing Clinical Trial with **ZENHALE** 200/5 and 100/5

This 26-week double-blind, randomized control trial evaluated 11,729 patients, 12 years of age and older, who received at least one dose of **ZENHALE** (100 mcg/5 mcg or 200/5 mcg, n=5868) or mometasone furoate monotherapy (100 mcg or 200 mcg, n=5861) each administered as 2 inhalations twice daily by metered dose inhalation aerosols. All patients had a diagnosis of persistent asthma for at least one year and had been receiving a stable dose of an asthma maintenance therapy for at least 4 weeks prior to randomization. The assigned dose level of inhaled corticosteroid was based on the patients' disease severity, considering their prior asthma medication and current level of asthma control. Patients also had a history of one to four asthma exacerbations requiring hospitalization or systemic corticosteroid use between 4 and 52 weeks prior to randomization, suggesting a future risk of asthma exacerbation. Prior asthma maintenance therapies were discontinued upon randomization. A broad range of asthmatics, with varying levels of treatment and incoming asthma control, were represented (Table 5). All treatment groups were balanced with regard to baseline characteristics; patients ranged from ages 12 to 88 years of age (median age 47 years); and were 66% female and 77% Caucasian.

Table 5. Baseline Characteristics by Incoming Asthma Treatment/Asthma Control

Group	(%)	Incoming Asthma Treatment/Asthma Control
1	29.3%	Not well controlled on daily short-acting beta agonist, leukotriene receptor antagonist, theophylline, or low-dose ICS OR controlled on low-dose ICS ± LABA or other therapies
2	32.3%	Not well controlled on daily low-dose ICS + LABA or other therapies OR controlled on medium-dose ICS ± LABA or other therapies
3	23.5%	Not well controlled on daily medium-dose ICS ± LABA or other therapies OR controlled on high-dose ICS monotherapy
4	14.8%	Controlled on daily high-dose ICS + LABA or other therapies
ICS = inhaled corticosteroid; LABA = long-acting beta$_2$ agonist; MF = mometasone furoate; MF/F = mometasone furoate/formoterol. Groups 1 and 2 received MF 100 mcg or MF/F 100 mcg/5 mcg, two inhalations, twice daily. Groups 3 and 4 received MF 200 mcg or MF/F 200 mcg/5 mcg, two inhalations, twice daily.		

The primary safety endpoint, a composite of Serious Asthma Outcomes (SAOs), defined as hospitalizations (≥24 hour stay), intubations (endotracheal), and deaths adjudicated by an independent committee as asthma-related was assessed by time-to-first event. Non-inferiority of **ZENHALE** to mometasone furoate monotherapy was demonstrated based on the 95% confidence interval upper limit of the hazard ratio less than 2.0 (Table 6), indicating that the addition of formoterol to mometasone furoate (**ZENHALE**) does not increase the risk of serious asthma-related events. All 71 (0.6%) of the serious asthma outcomes were hospitalizations; no asthma-related intubations (endotracheal); or asthma-related deaths were observed. The SAO rate in the adolescent subgroup (ages 12 to 17) was consistent with the overall population. Six (0.6%) SAOs occurred among the 1037 adolescent patients, with 2 (0.4%) in the **ZENHALE** arm and 4 (0.7%) in the mometasone furoate monotherapy arm.

Table 6. Primary Safety Results: Time-to-First Serious Asthma Outcome (SAO) and Components

First SAOs*	ZENHALE (%)	Mometasone furoate n (%)	Total n (%)	ZENHALE vs. Mometasone furoate	
Subjects in population	5868	5861	11,729	Hazard Ratio† (95% CI)	p-value†
Composite of All First SAOs	**39 (0.66)**	**32 (0.55)**	**71 (0.6)**	**1.22 (0.76, 1.94)**	**0.411**
Asthma-Related	39 (0.66)	32 (0.55)	71 (0.6)	1.22 (0.76,	ns

Hospitalizations				1.94)	
Asthma-Related Intubations	0	0	0	--	--
Asthma-Related Deaths	0	0	0	--	--

Results provided for all randomized patients who received at least one dose of **ZENHALE** (100 mcg/5 mcg and 200 mcg/5 mcg, two inhalations, prescribed twice daily) or mometasone furoate (100 mcg and 200 mcg, two inhalations, prescribed twice daily).

ns = non-significant p-value at the unadjusted two-sided alpha level of 0.05.

* For a given subject, the first SAO denotes first adjudicated event per subject.

† Based on the Cox proportional hazard model with covariates of treatment (ZENHALE vs. mometasone furoate) and inhaled corticosteroid dose level (100 mcg vs. 200 mcg), as treated.

The key efficacy endpoint, a composite of asthma exacerbation, defined as clinical deteriorations of asthma associated with systemic corticosteroid use for 3 consecutive days (or ≥1 depot injectable), emergency department visits <24 hours requiring systemic corticosteroid, or hospital stays of ≥24 hours, was also assessed by time-to-first event. A significant reduction in the risk of asthma exacerbation was demonstrated with **ZENHALE** versus mometasone furoate monotherapy based on the 95% confidence interval upper limit of the hazard ratio less than 1.0, achieving statistical significance (one-sided p-value <0.025) (Table 7). This outcome was primarily driven by systemic corticosteroid use (tablets, suspension or injection), which accounted for 87% (1296 of the total 1487 first asthma exacerbation events) of the total number of first asthma exacerbations. There was a 14% reduction in asthma exacerbations requiring systemic corticosteroids for subjects treated with **ZENHALE** compared to mometasone furoate monotherapy [0.86 (0.77 to 0.96), p=0.005]. Although not powered to allow for statistical analysis of treatment differences, the adolescent subgroup (ages 12 to 17) had a lower rate of exacerbations (9.9%) compared to the overall population (12.7%).

Table 7. Key Efficacy Results: Time-to-First Asthma Exacerbation and Components

First Asthma Exacerbations	**ZENHALE (%)**	**Mometasone furoate n (%)**	**Total n (%)**	**ZENHALE vs. Mometasone furoate**	
Subjects in population	5868	5861	11,729	Hazard Ratio* (95% CI)	p-value*
Composite of All First Asthma Exacerbations†	**708 (12.1)**	**779 (13.3)**	**1487 (12.7)**	**0.89 (0.80, 0.98)**	**0.021**
Used Systemic	606 (10.3)	690 (11.8)	1296	0.86 (0.77, 0.96)	0.005

Corticosteroid‡			(11.0)		
ED Visit <24 hours Requiring Systemic Corticosteroid§	67 (1.1)	64 (1.1)	131 (1.1)	1.03 (0.73, 1.45)	ns
Hospitalized ≥24 hours (in any healthcare facility)¶	35 (0.6)	25 (0.4)	60 (0.5)	1.38 (0.83, 2.31)	ns

Results consist of all randomized patients who received at least one dose of **ZENHALE** (100 mcg/5 mcg and 200 mcg/5 mcg, two inhalations, prescribed twice daily) or mometasone furoate (100 mcg and 200 mcg, two inhalations, prescribed twice daily). Follow-up time is censored 7 days after blinded treatment discontinuation.

ns = non-significant p-value at the unadjusted two-sided alpha level of 0.05.

* Based on the Cox proportional hazards model with covariates of treatment (**ZENHALE** vs. mometasone furoate) and inhaled corticosteroid dose level (100 mcg vs. 200 mcg), as treated.

† For a given subject, first asthma exacerbation denotes the first event per subject.

‡Systemic corticosteroids include tablets, suspension or injection for ≥3 consecutive days, OR ≥1 depot injectable.

§Emergency Department or any urgent care facility visit <24 hours where systemic corticosteroid is provided for asthma.

¶Hospital or other healthcare facility with a stay ≥24 hours for asthma.

Additional characterization of asthma exacerbation and related endpoints support the efficacy of mometasone alone and further reduction in clinical deterioration of asthma with the addition of formoterol. Only a small proportion of patients taking **ZENHALE** or mometasone furoate monotherapy had clinical deteriorations of asthma that were associated with emergency department visits (<24 hours) requiring systemic corticosteroids or hospitalization (≥24 hour stay) (Table 7). Overall improvement in asthma control with **ZENHALE** is also consistent with the overall reduction in rates of asthma exacerbation and systemic corticosteroid use across the study as well as less need for short-acting beta agonist or other add-on asthma therapies. Sustained improvement in asthma quality control scores were also observed across the study in both treatment arms, with larger differences seen in patients treated with **ZENHALE** (Table 8).

Table 8. Asthma Assessments Related to Asthma Exacerbation

	ZENHALE (%)	**Mometasone furoate n (%)**	**Relative Rate* or Difference in %† (95% CI)**	**p-value‡**
Asthma Exacerbation Rate	885 (12.1)	974 (13.3)	0.9 (0.8, 1.0)	0.037
Corticosteroid Rate	840 (11.5)	943 (12.9)	0.9 (0.8, 1.0)	0.018

Used >1 Canisters of SABA per Month	213 (3.6)	327 (5.6)	-1.9 (-2.7, -1.2)	<0.001
Additional Add-on Asthma Therapy§	268 (4.6)	326 (5.6)	-1.0 (-1.8, -0.2)	0.014
ACQ-6 Score <1 at Screening¶	2100 (35.8)	2171 (37.0)	-1.3 (-3.0, 0.5)	0.158
ACQ-6 Score <1 at Week 4	3644 (63.7)	3397 (59.8)	4.0 (2.2, 5.7)	<0.001
ACQ-6 Score <1 at Week 12	3779 (69.3)	3560 (66.3)	3.0 (1.2, 4.7)	<0.001
ACQ-6 Score <1 at Week 26	3770 (72.4)	3570 (70.0)	2.4 (0.7, 4.2)	0.007
ACQ-6 Score <1 at Last Visit#	3950 (70.3)	3799 (67.9)	2.4 (0.7, 4.1)	0.007

Results consist of all randomized patients who received at least one dose of **ZENHALE** (100 mcg/5 mcg and 200 mcg/5 mcg, two inhalations, prescribed twice daily) or mometasone furoate (100 mcg and 200 mcg, two inhalations, prescribed twice daily). Follow-up time is censored 7 days after blinded treatment discontinuation. P-values are descriptive and not controlled for multiplicity.

SABA = short-acting beta agonist; ACQ-6 = 6-item Asthma Control Questionnaire.

* Asthma Exacerbation and Corticosteroid Rates based on the negative binomial regression model accounting for the intercept and treatment effect.

†SABA Use, Additional Add-on Asthma Therapy, and ACQ-6 Scores based on the Miettinen & Nurminen method.

‡ Two-sided p-values (not adjusted for multiplicity).

§ Subjects who needed additional asthma treatment other than study-provided short-acting beta agonist or any study-provided systemic corticosteroid.

¶ Screening reflects the ACQ score used to determine the patient's ICS dose.

#Last Visit pertains to the final ACQ score for a subject and may occur prior to Week 26 for subjects who discontinue prematurely.

9 STORAGE CONDITION

Store at or below 30°C. Do not freeze.

10 PRESENTATIONS

ZENHALE 50/5 (120 puffs)

ZENHALE 100/5 (120 puffs)

ZENHALE 200/5 (120 puffs)

Not all presentations may be available

11 PRODUCT REGISTRANT

Organon Singapore Pte. Ltd.

150 Beach Road

#36-01/08 Gateway West

Singapore 189720

12 DATE OF REVISION

July 2022

ORGANON