- Combination drug for asthma treatment -

**Flutiform® 50 Aerosol 120 puffs**

**Flutiform® 125 Aerosol 120 puffs**

< Fluticasone propionate and Formoterol fumarate hydrate Aerosol >

Prescription-only drug
Caution: Use only pursuant to the prescription or directions of a physician, etc.

<table>
<thead>
<tr>
<th>Storage</th>
<th>Flutiform</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stored at room temperature</td>
<td>50 Aerosol 120 puffs</td>
</tr>
<tr>
<td>Approval No.</td>
<td>22500AMX01790000</td>
</tr>
<tr>
<td>Date of listing in the NHI reimbursement price</td>
<td>November 2013</td>
</tr>
<tr>
<td>Date of initial marketing in Japan</td>
<td>December 2014</td>
</tr>
<tr>
<td>International birth date</td>
<td>July 2012</td>
</tr>
</tbody>
</table>

**Cautions**
See “PRECAUTIONS FOR HANDLING”

**CONTRAINDICATIONS (Flutiform is contraindicated in the following patients.)**
1. Patients with infections for which no effective antimicrobial drugs exist or deep mycosis. (The effects of steroids may aggravate symptoms.)
2. Patients with a history of hypersensitivity to any of the ingredients of Flutiform.

**RELATIVE CONTRAINDICATIONS (As a general rule, Flutiform is contraindicated in the following patients. If the use of Flutiform is considered essential, it should be administered with care.)**
Patients with tuberculous diseases
(The effects of steroids may aggravate symptoms.)

**INDICATIONS**
Bronchial asthma
(In cases where concomitant use of inhaled corticosteroids and inhaled long-acting β₂-agonists is required)

**<Precautions>**
1. Flutiform should be used in cases where treatment with a combination of an inhaled corticosteroid and inhaled long-acting β₂-agonist is required.
2. Patients should be notified about the following: Flutiform does not rapidly ameliorate asthma attacks and thus should not be used for acute attacks. Acute attacks should be treated with other appropriate drugs including inhaled short-acting β₂-agonists.

**DOSAGE AND ADMINISTRATION**
The usual adult dosage for Flutiform 50 Aerosol (50 μg of fluticasone propionate and 5 μg of formoterol fumarate hydrate) is two inhalations (puffs), twice daily.
Flutiform 125 Aerosol (125 μg of fluticasone propionate and 5 μg of formoterol fumarate hydrate) should be inhaled 2-4 puffs, twice daily, depending on the symptoms.

**DESCRIPTION**
Product description

<table>
<thead>
<tr>
<th>Brand name</th>
<th>Flutiform</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 Aerosol 120 puffs</td>
<td>125 Aerosol 120 puffs</td>
</tr>
<tr>
<td>Amount of active ingredients in a single puff (amount measured in a container)</td>
<td>Fluticasone propionate 50 μg 125 μg Formoterol fumarate hydrate 5 μg 5 μg</td>
</tr>
<tr>
<td>Inactive ingredients</td>
<td>Sodium cromoglicate, dehydrated ethanol, 1,1,1,2,3,3,3-heptafluoropropane</td>
</tr>
<tr>
<td>Description</td>
<td>An inhaled aerosol preparation from which a constant amount of the drug solution is sprayed per actuation</td>
</tr>
</tbody>
</table>
Patients should be notified to use other appropriate drugs.

Continuous excessive use of Flutiform may induce arrhythmia, or Flutiform is not intended for rapid amelioration of bronchial exacerbation.

1. Patients must be made aware that excessive use of Flutiform may induce serious side effects such as arrhythmia and cardiac arrest, and should be notified not to use the drug at doses above the recommended dose regimens.

2. In cases where remission of symptoms is observed, Flutiform should be administered at the minimum dose required for treatment, and switching to other inhaled steroids should also be considered as necessary.

PRECAUTIONS

1. Careful Administration (Flutiform should be administered with care in the following patients.)

(1) Patients with infections
  [The effects of steroids may aggravate symptoms.]

(2) Patients with hyperthyroidism
  [Thyroid hormone secretion may increase.]

(3) Patients with hypertension
  [Blood pressure may increase.]

(4) Patients with heart disease
  [Effects on β₂ receptors may lead to worsening of symptoms.]

(5) Patients with diabetes mellitus
  [Glycogenolytic action and the effects of steroids may aggravate symptoms.]

(6) Patients with hypokalemia
  [Activation of the sodium-potassium adenosine triphosphatase and the resulting import of extracellular potassium into cells may lead to worsening of hypokalemia.]

(7) Patients with severe hepatic function disorder
  [Both ingredients of Flutiform, i.e., fluticasone propionate and formoterol, are mainly metabolized in the liver. The level of those in the blood may thus increase.]

2. Important Precautions

(1) Flutiform is not intended for rapid amelioration of bronchial asthma attacks that have already developed. Flutiform should be used daily with regularity.

(2) Asthmatic symptoms should be relatively stabilized before administering Flutiform. Basically, Flutiform should not be used particularly under status asthmaticus or a state of sudden asthma exacerbation.

(3) In patients with markedly increased bronchial mucus secretion, a mucoregulating drug should be used before inhalation of Flutiform until mucus secretion decreases to some extent, to ensure the effects of Flutiform inside the lung.

(4) Continuous excessive use of Flutiform may induce arrhythmia, or even cardiac arrest in some cases. Flutiform should not be administered at doses above the recommended dose regimens.

(5) Patients should be notified to use other appropriate drugs including inhaled short-acting β₂-agonists for acute attacks developing during treatment with Flutiform. Furthermore, in cases where the amount of other drugs used increases or they start lacking efficacy, patients should be notified to visit a medical institution and seek treatment from a physician as soon as possible, as such conditions may suggest that the asthma is not being adequately managed. These conditions may become life-threatening, and implementation of a more intensive steroid therapy (e.g., switching to a higher dose preparation of Flutiform) should thus be considered depending on symptoms in each patient.

(6) In cases where worsening of asthmatic symptoms associated with infections is observed, implementation of a more intensive steroid therapy and treatment of infection should be considered.

(7) Abrupt discontinuation of Flutiform may lead to a rapid exacerbation of asthma. Treatment should thus be stepped down with attention to asthmatic symptoms and then discontinued, if administration of Flutiform needs to be discontinued.

(8) Administration of inhaled steroids may induce systemic reactions (including Cushing’s syndrome, Cushingoid symptoms, adrenocortical suppression, pediatric growth retardation, decreased bone density, cataract, and glaucoma), although it is less likely compared to systemic steroids. The dose of inhaled steroids should thus be adjusted to the minimum dose that enables asthma control for each patient. Examinations should be performed on a regular basis particularly in cases of long-term use or high doses. If systemic reactions are confirmed as a result, appropriate measures, such as stepping down treatment while monitoring the patients’ asthmatic symptoms, should be taken.

(9) Reduction of systemic steroid doses should be performed slowly over time, after symptoms are confirmed to have stabilized after the start of inhalation of Flutiform. Methods of dose reduction for common steroids should be followed when reducing the doses.

(10) Patients on long-term or high-dose systemic steroid therapy may experience adrenocortical insufficiency. Adrenocortical function tests should thus be performed during the process of dose reduction and also after the withdrawal of systemic steroids, and sufficient attention should be paid to invasions such as trauma, surgeries, and serious infections. The dose of systemic steroids may be increased temporarily if necessary.

(11) Eosinophilia as a symptom of latent underlying Churg-Strauss syndrome develops on rare occasions after administration of inhaled steroids, including Flutiform. The symptom usually develops on dose reduction and withdrawal of systemic steroids, and no direct causality with Flutiform has been established. Changes in eosinophil counts and other symptoms of Churg-Strauss syndrome (e.g., vasculitis symptoms including numbness, pyrexia, arthralgia, and pulmonary infiltration) should be monitored carefully during treatment with Flutiform.

(12) Symptoms such as rhinitis, eczema, urticaria, giddiness, palpitations, malaise, facial flushing, and conjunctivitis may develop or worsen with dose reduction and withdrawal of systemic steroids. Appropriate measures should be taken if these symptoms occur.

(13) Development of systemic reactions to steroids (Cushing’s syndrome, suppression of adrenocortical function, etc.) has been reported in cases of concomitant use with ritonavir. Caution is thus warranted when using ritonavir concomitantly (see “Drug Interactions” section).

(14) Flutiform requires selection of an optimal dose according to asthmatic symptoms in each patient. Patients should thus be monitored on a regular basis during treatment with Flutiform.

3. Drug Interactions

Fluticasone propionate is mainly metabolized in the liver by cytochrome P-450 3A4 (CYP3A4), and formoterol is mainly metabolized in the liver by cytochrome P-450 3A4 (CYP3A4).
metabolized by glucuronic acid conjugation. (See “PHARMACOKINETICS” section.)

Precautions for coadministration (Flutiform should be administered with care when coadministered with the following drugs.)

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Signs, Symptoms, and Treatment</th>
<th>Mechanism and Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs with inhibitory effects on CYP3A4</td>
<td>Symptoms similar to those observed with systemic administration of adrenocorticosteroids may develop. Cushing’s syndrome, suppression of adrenocortical function, etc., with concomitant use of ritonavir and fluticasone propionate preparations in particular, has been reported.</td>
<td>Inhibition of CYP3A4 metabolism may result in an increase in the blood concentration of fluticasone propionate.</td>
</tr>
<tr>
<td>Catecholamines</td>
<td>Arrhythmia, or in some cases cardiac arrest, may develop. Developments of adverse reactions should be monitored carefully, and appropriate measures such as dose reduction or treatment discontinuation should be taken in cases where abnormalities are confirmed.</td>
<td>Concomitant use leads to increases in adrenergic stimuli. Arrhythmia may thus develop.</td>
</tr>
<tr>
<td>Xanthine derivatives</td>
<td>Arrhythmia due to hypokalemia may occur. Monitoring of serum potassium levels is desirable.</td>
<td>Xanthine derivatives increase adrenergic stimuli, and serum potassium levels may thus decrease further.</td>
</tr>
<tr>
<td>Steroids</td>
<td>Effects of formoterol may be reduced.</td>
<td>Beta receptors are competitively antagonized.</td>
</tr>
</tbody>
</table>

| Drugs known to induce QT interval prolongation | QT intervals may be prolonged, leading to increased risk of ventricular arrhythmia and other conditions. | Any of these drugs may induce QT interval prolongation. |

4. Adverse Reactions

In clinical studies conducted in Japan, adverse reactions (including abnormal laboratory values) were confirmed in 101 (21.4%) of a total of 472 patients subjected to the collection of adverse reactions. Main adverse reactions included “hoarseness” in 25 patients (5.3%), “blood creatine phosphokinase increased” in 10 patients (2.1%), “palpitations” in 6 patients (1.3%), “asthma” in 6 patients (1.3%), “stomatitis” in 5 patients (1.1%), and “pharyngitis” in 5 patients (1.1%).

1) Clinically significant adverse reactions

(1) Shock, anaphylaxis (incidence unknown)

Since shock and anaphylaxis (dyspnea, bronchospasm, generalized flushing, angioedema, urticaria, etc.) may occur, patients should be monitored carefully. In the event of such abnormalities, Flutiform should be discontinued, and appropriate measures should be taken.

(2) Serious decreases in serum potassium levels (incidence unknown)

“Serious decreases in serum potassium levels” have been reported with β_{2}-agonists. Furthermore, the serum potassium-lowering effects of β_{2}-agonists may be increased by coadministration of xanthine derivatives, steroids, and diuretics. Particular caution should thus be exercised in patients with severe asthma. In addition, hypoxemia may intensify the effects of decreases in serum potassium level on cardiac rhythm. In such cases, monitoring of serum potassium levels is desirable.

(3) Pneumonia (0.42%)

Since pneumonia may occur, patients should be monitored carefully. In the event of such an abnormality, Flutiform should be discontinued, and appropriate measures should be taken.

2) Other adverse reactions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral/respiratory</td>
<td>≥5%</td>
</tr>
<tr>
<td>Hoarseness</td>
<td>≥1 and &lt;5%</td>
</tr>
<tr>
<td>Oral and respiratory infections, oral and pharyngolaryngeal symptoms (pain and discomfort), asthma, stomatitis</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

Cardiovascular | Arrhythmia, palpitations |
Abnormal electrocardiogram, hypertension | Oral dryness |
Hepatic

γ-GTP increased, ALT (GPT) increased, blood bilirubin increased

Neuropsychiatric

Tremor, giddiness

Hypersensitivity

Rash, urticaria

Others

CK (CPK) increased

Blood cortisol decreased, white blood cell count increased, malaise, muscle spasms, chest discomfort

Note) Flutiform should be discontinued when these events develop.

5. Use in the Elderly

Since the physiological functions of elderly individuals are generally decreased, Flutiform should be administered carefully, observing the condition of the patient.

6. Use during Pregnancy, Delivery or Lactation

(1) Flutiform should only be used in pregnant women and women who may possibly be pregnant if the expected therapeutic benefits are evaluated to outweigh the possible risks of treatment.

(Fetal growth restriction and teratogenicity have been confirmed in rabbits with inhalation of fluticasone propionate ≥1.6 μg/kg and formoterol fumarate hydrate ≥0.16 μg/kg.)

(2) It is desirable to avoid the use of Flutiform during lactation. If there is no other choice but to use Flutiform, the patient should be directed to avoid breastfeeding.

(Excretion of fluticasone propionate and formoterol in breast milk has been reported in animal studies (in rats))

7. Pediatric Use

Safety of Flutiform in low birth weight infants, neonates, infants, and children has not been established (no clinical experience).

8. Overdosage

(1) Overdosage of formoterol fumarate hydrate may induce systemic reactions associated with the pharmacological action of β2-agonists, such as palpitations, tachycardia, arrhythmia, tremor, headaches and muscle spasms. In addition, decreased blood pressure, metabolic acidosis, hypokalemia, hyperglycemia, ventricular arrhythmia, cardiac arrest, etc., may develop as serious symptoms. If such symptoms are observed, Flutiform should be discontinued and proper measures should be taken.

(2) Overdose (doses higher than the usual dose) of fluticasone propionate may induce systemic reactions such as adrenocortical suppression.

Trauma, surgery, infection, rapid decrease in the dose of Flutiform, etc., may lead to acute adrenocortical insufficiency in patients with suppression of adrenocortical function. Dose reduction of Flutiform after an overdose should be performed slowly with careful management of the patient.

9. Precautions concerning Use

(1) Flutiform should only be used for oral inhalation.

(2) Before inhalation: When administering Flutiform, sufficient explanations on how to use the inhalation device, how to inhale the drug, etc., should be provided to the patient. (See “PRECAUTIONS FOR HANDLING” section.)

(3) After inhalation: To prevent oral candidiasis and hoarseness, patients should be instructed to gargle after inhaling Flutiform. However, those with difficulty gargling should be instructed to rinse orally instead of gargling.

10. Other Precautions

The following has been reported in a large-scale placebo-controlled study of another long-acting inhaled β2-agonist (salmeterol [aerosol formulation]) conducted in the United States:

In a 28-week, placebo-controlled, multi-center study in patients with asthma conducted in the United States, the number of respiratory-related deaths and life-threatening events in total, i.e., the primary endpoint, was significantly greater in the salmeterol group than in the placebo group in the African-American population, although no significant differences between groups were observed in the entire study population. Furthermore, the number of asthma-related deaths, i.e., a secondary endpoint, was significantly greater in the salmeterol group than in the placebo group. In the population of patients concomitantly using inhaled steroids, no significant differences between groups were noted in the primary or secondary endpoints.

PHARMACOKINETICS

1. Plasma Concentrations

(1) Single dose in healthy adults

Flutiform 50 Aerosol 2 inhalations per dose (fluticasone propionate 100 μg and formoterol fumarate hydrate 10 μg) or Flutiform 125 Aerosol 4 inhalations per dose (fluticasone propionate 500 μg and formoterol fumarate hydrate 20 μg) were administered twice daily for 7 days in 12 healthy adult men for each dosing. Plasma concentrations of fluticasone propionate and formoterol after the initial dose rapidly reached the maximum concentration (Cmax).
Figure 1 Plasma concentration of fluticasone propionate after a single dose of inhaled fluticasone propionate/formoterol fumarate hydrate (n=12, mean ± standard deviation #: n=11, # #: n=9)

Table 1 Pharmacokinetic parameters of inhaled fluticasone propionate and formoterol after a single dose

<table>
<thead>
<tr>
<th>Name of ingredient</th>
<th>Dose (µg)</th>
<th>Cmax (pg/mL)</th>
<th>tmax (hr)</th>
<th>AUC0-12 (pg·hr/mL)</th>
<th>tmax (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flutiform 50 Aerosol 2 inhalations per dose</td>
<td>fluticasone propionate</td>
<td>100</td>
<td>37.9 ±10.7</td>
<td>0.0833 ±0.033</td>
<td>228 ±91.2</td>
</tr>
<tr>
<td></td>
<td>formoterol fumarate hydrate</td>
<td>10</td>
<td>13.2 ±4.31</td>
<td>0.0833 ±0.033</td>
<td>44.4 ±6.62</td>
</tr>
<tr>
<td>Flutiform 125 Aerosol 4 inhalations per dose</td>
<td>fluticasone propionate</td>
<td>500</td>
<td>70.9 ±19.5</td>
<td>0.0833 ±0.033</td>
<td>395 ±155</td>
</tr>
<tr>
<td></td>
<td>formoterol fumarate hydrate</td>
<td>20</td>
<td>26.3 ±15.9</td>
<td>0.0833 ±0.033</td>
<td>64.4 ±26.5</td>
</tr>
</tbody>
</table>

(n=12 mean ± standard deviation, median value for tmax (minimum, maximum)

2. Distribution

Protein binding ratio of fluticasone propionate and formoterol in human plasma was 81%-95% and 61%-64%, respectively (in vitro study).

3. Metabolism and excretion

When 3H-labeled fluticasone propionate was administered orally at 1 mg or 16 mg in healthy volunteers (non-Japanese), 1-5% of the administered radioactivity was excreted in urine up to 168 hr after administration. The unchanged drug was not detected, and 17β-carboxylic acid metabolite and glucuronate conjugate were observed. In feces, approximately 90% or more of the administered radioactivity was excreted, and the unchanged drug and 17β-carboxylic acid metabolite, a main metabolite, were excreted.

When 3H-labeled formoterol 16 µg was administered by continuous intravenous infusion over 30 min immediately after oral administration of 3H-labeled formoterol 37 µg in healthy volunteers (non-Japanese), 62% of the administered radioactivity was excreted in urine and 24% was excreted in feces up to 168 hr after administration. The main metabolite in plasma and urine was glucuronate conjugate of formoterol, and O-demethylated glucuronate conjugate was also noted in urine.
4. Metabolic enzyme
CYP3A4 is involved in metabolism of fluticasone propionate to 17β-carboxylate, the main metabolite (in vitro study).\textsuperscript{5)} CYP2D6, 2C19, 2C9, and 2A6 are responsible for O-demethylation of formoterol.\textsuperscript{5)}

CLINICAL STUDIES
Clinical studies conducted in Japan
(1) In a randomized single-blinded parallel-group study in 455 adult patients with bronchial asthma, patients received 8-week treatment with Flutiform 50 Aerosol 2 inhalations per dose (fluticasone propionate 100 µg and formoterol fumarate hydrate 10µg) or fluticasone propionate 100 µg twice daily as control. The results of the study are shown in Table 3.\textsuperscript{8)}

Table 3 Changes in morning peak flow from baseline (FAS)

<table>
<thead>
<tr>
<th>Drug (Dose)</th>
<th>Baseline</th>
<th>Mean value up to end of 8th week of treatment</th>
<th>Changes ((%a))</th>
<th>Difference between groups (two-sided 95% confidence interval) (p) value\textsuperscript{a) b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flutiform 50 Aerosol 2 inhalations per dose (fluticasone propionate 100µg and formoterol fumarate hydrate 10µg)</td>
<td>349.7 ±84.8 (228)</td>
<td>380.2 ±90.3 (228)</td>
<td>30.5 ±30.1 (228)</td>
<td>[15.47, 25.80]</td>
</tr>
<tr>
<td>Control (fluticasone propionate 100µg)</td>
<td>344.2 ±81.0 (227)</td>
<td>353.6 ±81.1 (226)</td>
<td>9.9 ±25.9 (226)</td>
<td></td>
</tr>
</tbody>
</table>

Note) Mean ± standard deviation (n)
a) Covariance analysis model using treatment group and %peak flow at baseline as explanatory variables

(2) In a long-term use study in 244 adult patients with bronchial asthma, patients started to receive twice-daily treatment with Flutiform 50 Aerosol 2 inhalations per dose (fluticasone propionate 100 µg and formoterol fumarate hydrate 10 µg), Flutiform 125 Aerosol 2 inhalations per dose (fluticasone propionate 250 µg and formoterol fumarate hydrate 10 µg), or Flutiform 125 Aerosol 4 inhalations per dose (fluticasone propionate 500 µg and formoterol fumarate hydrate 20 µg), based on the doses of inhaled steroids that had been used in a run-in period. Doses were allowed to be increased or decreased according to symptoms, and treatment was continued for 52 weeks. Figure 3 below shows changes in evaluation parameters representing lung function.\textsuperscript{9)}

PHARMACOLOGY
1. Fluticasone
(1) Affinity to glucocorticoid receptors
Affinity of fluticasone to glucocorticoid receptors in human lung tissues was 0.5nmol/L.\textsuperscript{10,11)}

(2) Anti-inflammatory effects
1) Inhaled fluticasone inhibited antigen (ovalbumin [OVA])-induced increases in eosinophils, lymphocytes, and macrophage in bronchoalveolar lavage fluid (BALF) in guinea pigs sensitized with OVA.\textsuperscript{12)}

2) Inhaled fluticasone inhibited OVA-induced eosinophil infiltration in the tracheal epithelium and increase in airway constriction caused by methacholine in guinea pigs sensitized with OVA.\textsuperscript{13)}

2. Formoterol
(1) Affinity and selectivity to \(\beta_2\) receptors
Affinity of formoterol to \(\beta_2\) receptors was 8.63(-logK\textsubscript{D}) in cells expressing human receptors. Formoterol has 331 and 646 fold greater affinity to \(\beta_2\) receptors than to \(\beta_1\) (-logK\textsubscript{D}: 6.11) and \(\beta_3\) receptors (-logK\textsubscript{D}: 5.82), respectively.\textsuperscript{14)}

(2) Effects on asthmatic symptoms
Inhaled formoterol suppressed histamine-induced asthmatic symptoms in guinea pigs. Median effective dose (ED\textsubscript{50}) was 1/22 of that of oral administration.\textsuperscript{15)}

(3) Effects on airway constrictive reaction
Inhaled formoterol inhibited OVA-induced reduction in airway conductance (specific airway conductance [SGaw]) in immediate asthmatic reaction (IAR) and late asthmatic reaction (LAR) in guinea pigs sensitized with OVA, and inhibited rise in total cells, macrophage, eosinophils, neutrophils, and lymphocytes in BALF.\textsuperscript{16)}

3. Fluticasone and formoterol
Formoterol intensified glucocorticoid responsive element (GRE)-dependent transcription activation induced by fluticasone in human tracheal epithelial cell line (BEAS-2B).\textsuperscript{17)}

PHYSICOCHEMISTRY
Fluticasone propionate
Nonproprietary name: fluticasone propionate (JAN), fluticasone (INN)
Kyorin Pharmaceutical Co., Ltd.

Chemical name: S-Fluoromethyl 6α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-propionyloxandrost-1,4-diene-17β-carbothioate
Molecular formula: C₂₅H₃₁F₃O₅S
Molecular weight: 500.57
Melting point: 272-273°C
Description: Fluticasone propionate is a white or practically white powder. It is freely soluble in N,N-dimethylformamide, sparingly soluble in acetone and dichloromethane, slightly soluble in ethanol (96%), and practically insoluble in water.

Structural formula:

Formoterol Fumarate Hydrate
Nonproprietary name: formoterol fumarate hydrate (JAN), formoterol (INN)
Chemical name: N-(2-Hydroxy-5-{(1RS)-1-hydroxy-2-[(1RS)-2-(4-methoxyphenyl)-1-methylethylamino]ethyl}-phenyl)formamide hemifumarate monohydrate
Molecular formula: (C₁₉H₂₄N₂O₄)₂·C₄H₄O₄·2H₂O
Molecular weight: 840.91
Melting point: about 138°C (with decomposition)
Description: Formoterol Fumarate Hydrate occurs as a white to yellowish white, crystalline powder. It is freely soluble in acetic acid(100), soluble in methanol, very slightly soluble in water and in ethanol (95), and practically insoluble in diethyl ether.

Structural formula:

PRECAUTIONS FOR HANDLING
1. Patients should be provided with the instructions and instructed how to use the device.
2. Use of a spacer (assistive device for inhalation) is desirable for patients who have difficulties puffing and inhaling aerosol at the same time.
3. Patients should be instructed to shake the inhaler well before using.
4. Instruction for storage
   (1) Do not detach the inner aluminum container from the adapter.
   (2) Wipe well outside and inside of mouthpiece with dry cloth or tissue paper at least once or more a week to avoid clogging of a spray outlet, and keep the device clean.
   (3) Keep the aluminum container dry (wet container may cause clogging of a spray outlet)
   (4) Do not keep the inhaler in a place at 30°C or higher.
   (5) Do not throw the aluminum container into flame.
   (6) Follow the instruction on how to dispose of aluminum containers specified by local authorities.

PACKAGING
Flutiform 50 Aerosol 120 puffs: 1
Flutiform 125 Aerosol 120 puffs: 1

REFERENCES
2) Phase I and clinical pharmacological study of Flutiform (In-house data)

REQUEST FOR LITERATURE SHOULD BE MADE TO:
A request for in-house data mentioned in the REFERENCES can also be made to the following.
Kyorin Pharmaceutical Co., Ltd. Drug Information Center
6, Kanda surugadai 4-chome, Chiyoda-ku, Tokyo 101-8311, Japan
Tel. 0120-409341 (Toll-free)
9:00 to 17:00 (Monday through Friday excluding national holidays)

Manufactured and marketed by:
Kyorin Pharmaceutical Co., Ltd.
6, Kanda surugadai 4-chome, Chiyoda-ku, Tokyo 101-8311, Japan