June 2016 (4nd version)

| Standard Commodity Classification No. of Japan |
|---|
| 872259 |

- COPD treatment -

# Eklira® 400 μg Genuair® 30 doses
# Eklira® 400 μg Genuair® 60 doses

< Inhaled aclidinium bromide>

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

| Storage |
|---|
| Stored at room temperature |

| Expiration date |
|---|
| Three years from the date of production<br>(See the date indicated on the outer cases.) |

| Cautions |
|---|
| See "PRECAUTIONS FOR HANDLING" |

| | Eklira | |
|---|---|---|
| | 400 μg Genuair 30 doses | 400 μg Genuair 60 doses |
| Approval No. | 22700AMX00636000 | 22700AMX00637000 |
| Date of listing in the NHI reimbursement price | May 2015 | June 2016 |
| Date of initial marketing in Japan | May 2015 | June 2016 |
| International birth date | July 2012 | |

**CONTRAINDICATIONS (Eklira is contraindicated in the following patients.)**

1. Patients with angle-closure glaucoma
   [The anticholinergic effect may cause increased intraocular pressure and an aggravation of symptoms.]
2. Patients with dysuria due to prostatic hyperplasia, etc.
   [The anticholinergic effect may induce urinary retention.]
3. Patients with a medical history of hypersensitivity to any of the ingredients of this medicine

## DESCRIPTION

**Product description**

| Brand name | Eklira 400 μg Genuair 30 doses | Eklira 400 μg Genuair 60 doses |
|---|---|---|
| metered dose※ | Aclidinium bromide 400 μg ( Aclidinium 343 μg) | |
| Excipient | Lactose monohydrate | |
| Dosage form, description | A white or almost white inhalation granular powder | |

※amount measured in a container

## INDICATIONS

Amelioration of various symptoms due to airway obstructive disorders in patients with chronic obstructive pulmonary disease (COPD) (chronic bronchitis and emphysema).

**< PRECAUTIONS CONCERNING INDICATIONS >**

Eklira is indicated for long-term management of symptoms of COPD.
It should not be used in the treatment of an acute COPD exacerbation.

## DOSAGE AND ADMINISTRATION

Normally, the product is administered by inhalation twice daily (one inhalation of 400 μg of aclidinium bromide per administration) in adults.

## PRECAUTIONS

**1. Careful administration (Eklira should be administered with care in the following patients.)**

(1) Patients with cardiac failure, atrial fibrillation or extrasystoles, or a history of either of them
[Administration of this product may cause cardiac failure, atrial fibrillation or extrasystoles.]
(2) Patients with prostatic hyperplasia
[The anticholinergic effect may cause dysuria.]

**2. Important precautions**

(1) As with other inhalation therapies, the administration of Eklira may cause paradoxical bronchospasm. If this occurs, treatment with Eklira should be immediately discontinued, and appropriate treatment should be provided.
(2) Eklira should not be used for the treatment of acute aggravation. Continuous treatment with Eklira is necessary to stabilize COPD symptoms. However, if the recommended regimen does not show adequate efficacy, Eklira is not considered to be an appropriate therapy; therefore, treatment with Eklira should be discontinued.

**3. Adverse reactions**

In the Japanese clinical studies, adverse reactions (including abnormal laboratory values) were reported in 40/442 subjects (9.0%). Major adverse reactions included

arrhythmia in 4 cases (0.9%), dizziness in 4 cases (0.9%), blood creatine phosphokinase increased in 3 cases (0.7%), and glucose urine present in 3 cases (0.7%).
In the overseas clinical studies, adverse reactions were reported in 260/2700 subjects (9.6%). Major adverse reactions included dry mouth in 28 cases (1.0%), headache in 26 cases (1.0%), and cough in 18 cases (0.7%). (At approval)

**(1) Clinically significant adverse reaction (similar drugs)**

Atrial fibrillation (frequency unknown)
Since administration of a similar drug (anticholinergic drugs) has been reported to induce atrial fibrillation, if an abnormal finding is observed, administration of this drug should be discontinued and appropriate measures should be taken.

**(2) Other adverse reactions**

| | ≥0.5% | Frequency unknown* |
|---|---|---|
| Respiratory | Dysphonia, oropharyngeal discomfort, cough* | Nasopharyngitis, sinusitis, rhinitis |
| Investigations | Glucose urine present, creatine phosphokinase increased, blood potassium increased | |
| Cardiovascular | Arrhythmia | |
| Gastrointestinal | Constipation, dry mouth* | Diarrhoea, toothache, vomiting |
| Skin | | Rash, pruritus |
| Others | Dizziness, headache* | Vision blurred, fall, urinary retention, hypersensitivity, angioedema |

* Adverse reactions reported in overseas.

**4. Use in the elderly**

Since physiological functions are generally reduced in the elderly, these products should be administered with care.

**5. Use during pregnancy, delivery or lactation**

(1) Eklira should be used in pregnant women or women who may possibly pregnant only if the expected therapeutic benefits outweigh the possible risks associated with the treatment..
[The safety of Eklira during pregnancy has not been established. Animal studies (rats) have shown that aclidinium bromide is transferred to fetus.]

(2) It is recommended to avoid its administration to nursing mothers. When the administration of Eklira is necessary, nursing mothers should discontinue breastfeeding during the treatment.
[Animal studies (rats) have shown that the drug is excreted into breast milk.]

**6. Pediatric use**

The safety of Eklira in low-birth weight infants, neonates, nursing infants, infants, or children has not been established (no clinical experience).

**7. Overdose**

Signs/Symptoms: Overdose of this product may induce anticholinergic signs and symptoms (dry mouth, palpitations, etc).
Treatment: If any of these symptoms appears, supportive and symptomatic treatment should be provided and, as needed, the patient should be monitored.

**8. Precautions concerning use**

(1) Eklira should be used only for inhalation through the mouth.

(2) Appropriate use of the product, such as how to use the inhaler and how to inhale, should be thoroughly explained to patients (see "PRECAUTIONS FOR HANDLING").

**9. Other precautions**

The combination use of Eklira with other anticholinergic bronchodilators is not recommended, as no clinical data are available on their combination use, and their efficacy and safety have not been established.

## PHARMACOKINETICS

**1. Plasma concentrations**

**(1) Single oral inhalation administration**

Following a single inhalation of aclidinium bromide (400 μg) in 13 COPD patients, plasma concentrations of aclidinium bromide rapidly reached the $C_{max}$ (Figure 1, Table 1)[1].

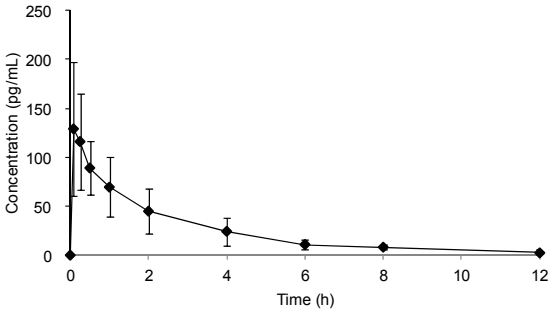



Figure 1 Changes in Plasma Concentrations Versus Time Profiles of Aclidinium Bromide Following Single Inhalation (n = 13, mean ± standard deviation)

Table 1 Pharmacokinetic Parameters Following Single Inhaled Administration of Aclidinium Bromide

| Dose | $C_{max}$ (pg/mL) | $t_{max}$ (hr) | $AUC_{inf}$ (pg·hr/mL) | $t_{1/2}$ (hr) |
|---|---|---|---|---|
| 400 μg | 144 ± 57.0 | 0.340 ± 0.395 | 330 ± 115 | 4.91 ± 4.49 |

(n = 13, mean ± standard deviation)

**(2)Multiple oral inhalation administration**

Following one inhalation of aclidinium bromide (400 μg) twice daily for 7 days in 13 COPD patients, plasma concentrations of aclidinium bromide had reached the steady state by the last inhalation in Day 7. The steady-state $C_{max}$ and $AUC_{\tau}$ were 1.77-fold of those following the single administration (Table 2)[1].

Table 2 Pharmacokinetic Parameters of Aclidinium Bromide After the Last Dose Following Multiple Inhaled Administration for 7 Days

| Dose | $C_{max}$ (pg/mL) | $t_{max}$ (hr) | $AUC_{\tau}$ (pg·hr/mL) | $t_{1/2}$ (hr) |
|---|---|---|---|---|
| 400 μg | 224 ± 93.6 | 0.212 ± 0.267 | 482 ± 121 | 13.6 ± 9.11 |

(n = 13, mean ± standard deviation)

**2. Absorption**

Following the single inhalation of aclidinium bromide (200 μg) in healthy adult subjects (non-Japanese), the absolute bioavailability was below 5%[2] (overseas data).

**3. Distribution**

Following the single inhalation of aclidinium bromide (200 μg) in healthy adult subjects (non-Japanese), whole-lung deposition of aclidinium bromide to the dose was 30.1%.[3] (overseas data).

**4. Metabolism**

*In vitro* studies have shown that the major metabolites of aclidinium bromide were alcohol and carboxylic acid metabolites. Hydrolyses of the ester bonds proceeded both enzymatically and nonenzymatically. In the enzymatic hydrolysis, plasma butyrylcholinesterase was suggested to be the main esterase involved[4].

The major human plasma metabolites were alcohol and carboxylic acid metabolites formed by the hydrolysis of ester binding of aclidinium bromide. In excreta, hydroxylated metabolites of the alcohol metabolite and reductants of the carboxylic acid metabolite were recovered[5] (overseas data).

**5. Excretion**

Following the single intravenous administration of $^{14}C$-radiolabelled aclidinium bromide (400 μg) in healthy adult subjects (non-Japanese), 65% of the dose was excreted in the urine and 33% in the feces. One percent of the dose was excreted as unchanged aclidinium bromide in the urine, and the residuals were excreted as hydrolysis metabolites[5] (overseas data).

**6. Drug interactions**

*In vitro* drug interaction studies have shown that aclidinium bromide and its major metabolites of alcohol metabolite and carboxylic acid metabolite did not inhibit the major CYP isozymes in substrate concentration of up to 100 μmol/L except that aclidinium bromide inhibited CYP2D6 ($IC_{50}$ value of 2.4 μmol/L) and CYP3A4/5 ($IC_{50}$ value of approx. 90 μmol/L) and that alcohol metabolite inhibited CYP2D6 ($IC_{50}$ value of 20.6 μmol/L). The investigation of CYP induction using cultured human liver cells have shown that aclidinium bromide, alcohol metabolite, and carboxylic acid metabolite did not exhibit induction effect on CYP 1A2, 2B6, 2C8, 2C9, 2C19, and 3A4/5 up to the concentration of 2.30, 3.80, and 172 nmol/L, respectively[6]. Aclidinium bromide inhibited on butyrylcholinesterase (Ki value of 2.7 μmol/L)[4]. Also, aclidinium bromide did not inhibit P-glycoprotein up to the concentration of 47.8 μmol/L)[7].

**7. Pharmacokinetics in patients with renal dysfunction**

Although elimination rate of aclidinium bromide in the urine decreased (healthy people, 0.09%; patients with moderate renal dysfunction, 0.06%; patients with severe renal dysfunction, 0.02%) following the single inhalation of aclidinium bromide (400 μg) in patients with renal dysfunction (non-Japanese), no clear difference was observed in $C_{max}$ and AUC between the healthy people and patients with renal dysfunction[8] (overseas data).

**8. Pharmacokinetics in the elderly**

Following the single inhalation of aclidinium bromide (400μg) in non-elderly COPD patients (ages between 40 and 59[9]) and elderly COPD patients (ages over 70), no clear difference was observed in proportions of $C_{max}$ and AUC between the non-elderly and the elderly, which were 86.4% and 88.5%, respectively[9] (overseas data).

**CLINICAL STUDIES**

**1. Japanese clinical study**

4-week study

In a randomized, placebo-controlled, double-blind, dose-finding study in 384 COPD patients, one inhalation of aclidinium bromide at 100 μg, 200 μg, or 400 μg was administered twice daily for 4 weeks. As a result, there was a statistically significant difference observed in changes in trough $FEV_1$ from the baseline after 4 weeks between the aclidinium bromide 400 μg and placebo groups, as shown in Table 3.[10]

Table 3 Changes (L) in Trough $FEV_1$ from Baseline to Week 4 (Full Analysis Set)

| | Aclidinium bromide 400 μg | Placebo |
|---|---|---|
| Baseline | 1.307 ± 0.422 (93) | 1.313 ± 0.453 (101) |
| After 4 weeks | 1.387 ± 0.431 (93) | 1.296 ± 0.461 (99) |
| Changes from Baseline | 0.080 ± 0.158 (93) | −0.024 ± 0.143 (99) |
| Difference from placebo | 0.105 [0.059, 0.150] p < 0.0001 | |

| | |
|---|---|
| [95% CI*][a)]<br>p-value[a)] | |

mean ± standard deviation (cases)

a) Analysis of variance model with treatment group as explaining variable.

**2. Overseas clinical studies**

In a randomized, placebo-controlled, double-blind study in COPD patients (non-Japanese), one inhalation of aclidinium bromide at 400 μg was administered twice daily for 24 weeks. As a result, there was a statistically significant difference observed in changes in trough $FEV_1$ from the baseline after 24 weeks between the aclidinium bromide 400 μg and placebo groups, as shown in Table 4. One inhalation of aclidinium bromide (400 μg) twice daily provided clinically meaningful improvement in the disease-specific health-related QOL (assessed using St. George's Respiratory Questionnaire), breathlessness (assessed using transitional dyspnea index), and the frequency of exacerbation of COPD in comparison with the placebo group[11] (overseas data).

Table 4 Changes (L) in Trough $FEV_1$ from Baseline to Week 24 (Intention to Treat)

| | Aclidinium bromide 400 μg | Placebo |
|---|---|---|
| Baseline | 1.508 ± 0.525 (269) | 1.500 ± 0.489 (273) |
| After 24 weeks | 1.573 ± 0.537 (269) | 1.442 ± 0.502 (273) |
| Changes from Baseline | 0.066 ± 0.274 (269) | −0.058 ± 0.244 (273) |
| Difference from placebo [95% CI*][a)]<br>p-value[a)] | 0.128 [0.085, 0.170]<br>p < 0.0001 | |

mean ± standard deviation (cases)

a) Analysis of covariance model with treatment group, sex, baseline $FEV_1$ and age as explaining variables.

## PHARMACOLOGY

**1. Mechanism of action**

Aclidinium bromide is a long-acting muscarinic receptor antagonist. It has potent affinities for all muscarine receptors subtypes ($M_1$ to $M_5$) and thus exhibits bronchodilatory efficacy. These affinities were comparable with that of tiotropium bromide.

Dissociation of aclidinium bromide from the $M_3$ receptor was slower than that from the $M_2$ receptor[12].

**2. Inhibition of tracheal contraction**

Aclidinium bromide inhibited carbachol-induced tracheal contraction in isolated guinea pig trachea[12].

**3. Onset and durability of action**

Aclidinium bromide inhibited acetylcholine-induced tracheal contraction in guinea pigs. The onset of action of aclidinium bromide was faster than that of tiotropium bromide and comparable with that of ipratropium bromide. The duration of action of aclidinium bromide was shorter than that of tiotropium bromide and longer than that of ipratropium bromide[12].

## PHYSICOCHEMISTRY

Nonproprietary name: aclidinium bromide

Chemical name: (3*R*)-3-[2-Hydroxy-2,2-di(thiophen-2-yl)acetyloxy]-1-(3-phenyloxypropyl)-1-azoniabicyclo[2.2.2]octane bromide

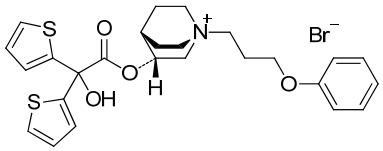
Molecular formula: $C_{26}H_{30}BrNO_4S_2$

Molecular weight: 564.56

Melting point: Approximately 224°C to 229°C

Description: A white or almost white powder. It is sparingly soluble in methanol, very slightly soluble in water and in ethanol, practically insoluble in acetone, ethyl acetate, tetrahydrofuran, and toluene.

Structural formula:




## PRECAUTIONS FOR HANDLING

1. At prescription

Supply user information to patients and instruct how to use Eklira when providing this product to patients.

2. Precautions for storage

(1) Always close the cap after use.

(2) Instruct patients to not put a high-intensity impact on the product or break the product into pieces.

(3) Eklira should be disposed as per the Disposal Law stipulated by the local authority.

## APPROVAL CONDITIONS

Formulate a risk management plan for drugs, and implement the plan appropriately.

## PACKAGING

Eklira 400 μg Genuair, 30 inhalation: 1

Eklira 400 μg Genuair, 60 inhalation: 1

## REFERENCES

1) Atsushi Nagai, et al., *J. Clin. Therp. Med.*, **31(3)**, 197, 2015

2) Stephan Ortiz., et al., *J.Clin.Pharmacol*., **52**, 819, 2012.

3) S.P. Newman., et al., *Respiration*, **78**, 322, 2009.

4) Joan Albertí., et al., *Drug Metab.Dispos*., **38(7)**, 1202, 2010.

5) Stephan Ortiz., et al., *Biopharm Drug Dispos*., **33(1)**, 39, 2012.

6) Investigation of Effect of Acliginium Bromide on P-450 Metabolizing Enzymes (internal material).

7) Investigation of Transportation by and Inhibitory Activity for P-glycoprotein of Aclidinium Bromide (internal material).

8) Karin Schmid., et al., *Clin.Therap*., **32**(10), 1798, 2010.

9) Stephan de la Motte., et al., *Int. J. Pharmacol.Thir*., **50**(6), 403, 2012.
10) Koichiro Tastumi, et al., *J. Clin. Therp. Med.*, **31(3)**, 207, 2015.
11) Jones PW., et al., *Eur. Respir. J.*, **40**(4),830, 2012.
12) Gavaldà A., et al., *J.Pharmacol.Exp.Ther.*, **331**, 740, 2009.

**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 17:30 (Monday through Friday excluding national holidays)

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