

# ARCAPTA NEOHALER- indacaterol maleate capsule

## Sunovion Pharmaceuticals Inc.

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### HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ARCAPTA NEOHALER safely and effectively. See full prescribing information for ARCAPTA NEOHALER. ARCAPTA® NEOHALER® (indacaterol) inhalation powder, for oral inhalation use  
Initial U.S. Approval: 2011

### INDICATIONS AND USAGE

ARCAPTA NEOHALER is a long-acting beta<sub>2</sub>-adrenergic agonist (LABA) indicated for the long-term, once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD). (1)

#### Limitations of Use

- ARCAPTA NEOHALER is not indicated to treat acute deteriorations of COPD. (1)
- ARCAPTA NEOHALER is not indicated for asthma. (1)

### DOSAGE AND ADMINISTRATION

For oral inhalation only. Do not swallow ARCAPTA capsule. ARCAPTA capsules should **always** be used with the NEOHALER inhaler **only**. (2.1)

Maintenance treatment of COPD: 75 mcg of indacaterol (contents of one ARCAPTA capsule) by oral inhalation once daily, using the NEOHALER inhaler. (2.2)

### DOSAGE FORMS AND STRENGTHS

Inhalation powder: 75 mcg of indacaterol per capsule for use with NEOHALER device. (3)

### CONTRAINDICATIONS

- Use of a LABA, including ARCAPTA NEOHALER, without an inhaled corticosteroid is contraindicated in patients with asthma. (4)
- ARCAPTA NEOHALER is contraindicated in patients with a history of hypersensitivity to indacaterol or to any of the ingredients. (4)

### WARNINGS AND PRECAUTIONS

- LABA as monotherapy (without an inhaled corticosteroid) for asthma increases the risk of serious asthma-related events. (5.1)
- Do not initiate in acutely deteriorating COPD patients. (5.2)
- Do not use for relief of acute symptoms. Concomitant short-acting beta<sub>2</sub>-agonists (SABAs) can be used as needed for acute relief. (5.2)
- Do not exceed the recommended dose. Excessive use or use in conjunction with other medications containing LABA can result in clinically significant cardiovascular effects and may be fatal. (5.3)
- Immediate hypersensitivity reactions may occur. Discontinue immediately. (5.4)
- Life-threatening paradoxical bronchospasm can occur. Discontinue immediately. (5.5)
- Use with caution in patients with cardiovascular or convulsive disorders, thyrotoxicosis or sensitivity to sympathomimetic drugs. (5.6, 5.7)

### ADVERSE REACTIONS

Most common adverse reactions (≥ 2% and more common than placebo) are cough, oropharyngeal pain, nasopharyngitis, headache, and nausea. (6)

**To report SUSPECTED ADVERSE REACTIONS, contact Novartis Pharmaceuticals Corporation at 1-888-669-6682 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).**

### DRUG INTERACTIONS

- Other adrenergic drugs may potentiate effect: Use with caution. (5.2, 7.1)
- Xanthine derivatives, steroids, diuretics, or non-potassium sparing diuretics may potentiate hypokalemia or electrocardiogram (ECG) changes. Use with caution. (7.2, 7.3)
- Monoamine oxidase inhibitors, tricyclic antidepressants, and drugs that prolong QTc interval may potentiate effect on cardiovascular system. Use with extreme caution. (7.4)
- Beta-blockers may decrease effectiveness: Use with caution and only when medically necessary. (7.5)

**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**

**Revised: 7/2021**

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## **FULL PRESCRIBING INFORMATION**

### **1 INDICATIONS AND USAGE**

ARCAPTA NEOHALER is indicated for long-term, once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD).

#### Limitations of Use

- ARCAPTA NEOHALER is not indicated to treat acute deteriorations of COPD [see *Warnings and Precautions (5.2)*].
- ARCAPTA NEOHALER is not indicated to treat asthma. The safety and effectiveness of ARCAPTA NEOHALER in asthma have not been established.

### **2 DOSAGE AND ADMINISTRATION**

#### **2.1 Administration Overview**

ARCAPTA capsules must not be swallowed as the intended effects on the lungs will not be obtained. The contents of ARCAPTA capsules are only for oral inhalation and should only be used with the NEOHALER device.


ARCAPTA capsules must always be stored in the blister, and only removed immediately before use.

#### **2.2 Recommended Dosage for Chronic Obstructive Pulmonary Disease**

The recommended dosage of ARCAPTA NEOHALER is the contents of one 75 mcg ARCAPTA capsule once daily by oral inhalation (at same time of day), using the NEOHALER inhaler.

If a dose is missed, the next dose should be taken as soon as it is remembered. Do not use ARCAPTA NEOHALER more than one time every 24 hours.

### **3 DOSAGE FORMS AND STRENGTHS**

Inhalation powder: ARCAPTA capsule contains 75 mcg indacaterol in hard gelatin capsule with black product code "IDL 75" above a bar printed on one side of the capsule and the logo "R  R" printed on the other side.

### **4 CONTRAINDICATIONS**

ARCAPTA NEOHALER is contraindicated in:

- use of a long-acting beta<sub>2</sub>-adrenergic agonist (LABA), including ARCAPTA NEOHALER, without an inhaled corticosteroid, in patients with asthma [see *Warnings and Precautions (5.1)*]. ARCAPTA NEOHALER is not indicated for the treatment of asthma.
- in patients with a history of hypersensitivity to indacaterol or to any of the ingredients [see *Warnings and Precautions (5.4)*].

## **5 WARNINGS AND PRECAUTIONS**

### **5.1 Serious Asthma-Related Events - Hospitalizations, Intubations, Death**

The safety and efficacy of ARCAPTA NEOHALER in patients with asthma have not been established. ARCAPTA NEOHALER is not indicated for the treatment of asthma [see *Contraindications (4)*].

Use of (LABAs), such as indacaterol, the active ingredient in ARCAPTA NEOHALER, as monotherapy [without inhaled corticosteroids (ICS)] for asthma is associated with an increased risk of asthma-related death. Available data from controlled clinical trials also suggest that use of LABA as monotherapy increases the risk of asthma-related hospitalization in pediatric and adolescent patients. These findings are considered a class effect of LABA monotherapy. When LABA are used in fixed-dose combination with ICS, data from large clinical trials do not show a significant increase in the risk of serious asthma-related events (hospitalizations, intubations, death) compared with ICS alone.

A 28-week, placebo-controlled US study comparing the safety of another LABA (salmeterol) with placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths in patients receiving salmeterol (13/13176 in patients treated with salmeterol vs. 3/13179 in patients treated with placebo; RR 4.37, 95% CI 1.25, 15.34). The increased risk of asthma-related death is considered a class effect of LABAs, including ARCAPTA NEOHALER.

No study adequate to determine whether the rate of asthma-related death is increased in patients treated with ARCAPTA NEOHALER has been conducted. Serious asthma-related events, including death, were reported in clinical studies with ARCAPTA NEOHALER. The sizes of these studies were not adequate to precisely quantify the differences in serious asthma exacerbation rates between treatment groups [see *Adverse Reactions (6.2)*].

Available data do not suggest an increased risk of death with use of LABA in patients with COPD.

### **5.2 Deterioration of Disease and Acute Episodes**

ARCAPTA NEOHALER should not be initiated in patients with acutely deteriorating COPD, which may be a life-threatening condition. ARCAPTA NEOHALER has not been studied in patients with acutely deteriorating COPD. The use of ARCAPTA NEOHALER in this setting is inappropriate.

ARCAPTA NEOHALER should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. ARCAPTA NEOHALER has not been studied in the relief of acute symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled

short-acting beta<sub>2</sub>-agonist (SABA).

When beginning ARCAPTA NEOHALER, patients who have been taking inhaled, SABAs on a regular basis (e.g., four times a day) should be instructed to discontinue the regular use of these drugs and use them only for symptomatic relief of acute respiratory symptoms. When prescribing ARCAPTA NEOHALER, the healthcare provider should also prescribe an inhaled, SABA and instruct the patient on how it should be used. Increasing inhaled beta<sub>2</sub>-agonist use is a signal of deteriorating disease for which prompt medical attention is indicated.

COPD may deteriorate acutely over a period of hours or chronically over several days or longer. If ARCAPTA NEOHALER no longer controls the symptoms of bronchoconstriction, or the patient's inhaled, SABA becomes less effective or the patient needs more inhalation of SABA than usual, these may be markers of deterioration of disease. In this setting, a reevaluation of the patient and the COPD-treatment regimen should be undertaken at once. Increasing the daily dosage of ARCAPTA NEOHALER beyond the recommended dose is not appropriate in this situation.

### **5.3 Avoid Excessive Use of ARCAPTA NEOHALER and Avoid Use With Other Long-Acting Beta<sub>2</sub>-Adrenergic Agonists**

As with other inhaled beta<sub>2</sub>-adrenergic drugs, ARCAPTA NEOHALER should not be used more often, at higher doses than recommended, or in conjunction with other medications containing LABAs, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs.

### **5.4 Hypersensitivity Reactions, Including Anaphylaxis**

Immediate hypersensitivity reactions may occur after administration of ARCAPTA NEOHALER. If signs suggesting allergic reactions (in particular, difficulties in breathing or swallowing, swelling of tongue, lips and face, urticaria, skin rash, anaphylaxis) occur, ARCAPTA NEOHALER should be discontinued immediately and alternative therapy instituted.

### **5.5 Paradoxical Bronchospasm**

As with other inhaled beta<sub>2</sub>-agonists, ARCAPTA NEOHALER may produce paradoxical bronchospasm that may be life-threatening. If paradoxical bronchospasm occurs, ARCAPTA NEOHALER should be discontinued immediately and alternative therapy instituted.

### **5.6 Cardiovascular Effects**

ARCAPTA NEOHALER, like other beta<sub>2</sub>-agonists, can produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, or symptoms. If such effects occur, ARCAPTA NEOHALER may need to be discontinued. In addition, beta-agonists have been reported to produce electrocardiogram (ECG) changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression, although the clinical significance of these findings is unknown. Therefore, ARCAPTA NEOHALER, like other sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

## 5.7 Coexisting Conditions

ARCAPTA NEOHALER, like other sympathomimetic amines, should be used with caution in patients with convulsive disorders or thyrotoxicosis, and in patients who are unusually responsive to sympathomimetic amines. Doses of the related beta<sub>2</sub>-agonist albuterol, when administered intravenously, have been reported to aggravate pre-existing diabetes mellitus and ketoacidosis.

## 5.8 Hypokalemia and Hyperglycemia

Beta<sub>2</sub>-agonist medications may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects [see *Clinical Pharmacology (12.2)*]. The decrease in serum potassium is usually transient, not requiring supplementation. Inhalation of high doses of beta<sub>2</sub>-adrenergic agonists may produce increases in plasma glucose.

Clinically notable decreases in serum potassium or changes in blood glucose were infrequent during clinical studies with long-term administration of ARCAPTA NEOHALER with the rates similar to those for placebo controls. ARCAPTA NEOHALER has not been investigated in patients whose diabetes mellitus is not well-controlled.

## 6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described in greater detail elsewhere in the labeling:

- Serious Asthma-Related Events – Hospitalizations, Intubations, Death [see *Warnings and Precautions (5.1)*]
- Paradoxical Bronchospasm [see *Warnings and Precautions (5.5)*]
- Hypersensitivity Reactions, including Anaphylaxis [see *Contraindications (4), Warnings and Precautions (5.4)*]
- Cardiovascular Effects [see *Warnings and Precautions (5.6)*]

### 6.1 Clinical Trials Experience in Chronic Obstructive Pulmonary Disease

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The ARCAPTA NEOHALER safety database reflects exposure of 2516 patients to ARCAPTA NEOHALER at doses of 75 mcg or greater for at least 12 weeks in six confirmatory randomized, double-blind, placebo and active-controlled clinical trials [see *Clinical Studies (14)*]. In these trials, 449 patients were exposed to the recommended dose of 75 mcg for up to 3 months, and 144, 583, and 425 COPD patients were exposed to a dose of 150, 300, or 600 mcg for one year, respectively. Overall, patients had a mean pre-bronchodilator forced expiratory volume in one second (FEV<sub>1</sub>) percent predicted of 54%. The mean age of patients was 64 years, with 47% of patients aged 65 years or older, and the majority (88%) was Caucasian.

In these six clinical trials, 48% of patients treated with any dose of ARCAPTA NEOHALER reported an adverse reaction compared with 43% of patients treated with placebo. The proportion of patients who discontinued treatment due to adverse reaction was 5% for ARCAPTA NEOHALER-treated patients and 5% for placebo-treated patients. The most

common adverse reactions that lead to discontinuation of ARCAPTA NEOHALER were COPD and dyspnea.

The most common serious adverse reactions were COPD exacerbation, pneumonia, angina pectoris, and atrial fibrillation, which occurred at similar rates across treatment groups.

Table 1 displays adverse drug reactions reported by at least 2% of patients (and higher than placebo) during a 3-month exposure at the recommended 75 mcg once-daily dose. Adverse drug reactions are listed according to the Medical Dictionary for Regulatory Activities [(MedDRA), version 13.0] system organ class and sorted in descending order of frequency.

**Table 1: Number and Frequency of Adverse Drug Reactions Greater Than 2% (and Higher Than Placebo) in COPD Patients Exposed to ARCAPTA NEOHALER 75 mcg for Up to 3 Months in Multiple Dose, Controlled Trials**

	<b>Indacaterol 75 mcg once daily</b>	<b>Placebo</b>
	<b>n = 449</b>	<b>n = 445</b>
Adverse reaction	<b>n (%)</b>	<b>n (%)</b>
Respiratory, thoracic and mediastinal disorders		
- Cough	29 (6.5)	20 (4.5)
- Oropharyngeal pain	10 (2.2)	3 (0.7)
Infections and infestations		
- Nasopharyngitis	24 (5.3)	12 (2.7)
Nervous system disorders		
- Headache	23 (5.1)	11 (2.5)
Gastrointestinal disorders		
- Nausea	11 (2.4)	4 (0.9)

In these trials, the overall frequency of all cardiovascular adverse reactions was 2.5% for ARCAPTA NEOHALER, 75 mcg and 1.6% for placebo during a 3-month exposure. There were no frequently occurring specific cardiovascular adverse reactions for ARCAPTA NEOHALER 75 mcg (frequency at least 1% and greater than placebo).

Additional adverse drug reactions reported in greater than 2% (and higher than on placebo) in patients dosed with 150 mcg, 300 mcg, or 600 mcg for up to 12 months were as follows:

- Musculoskeletal and Connective Tissue Disorders: muscle spasm, musculoskeletal pain
- General Disorders and Administration-site Conditions: edema peripheral
- Metabolism and Nutrition Disorder: diabetes mellitus, hyperglycemia
- Infections and Infestations: sinusitis, upper respiratory tract infection

#### Cough Experienced Post-Inhalation

In the clinical trials, health care providers observed during clinic visits that an average of 24% of patients experienced a cough on at least 20% of visits following inhalation of the recommended 75 mcg dose of ARCAPTA NEOHALER compared to 7% of patients

receiving placebo. The cough usually occurred within 15 seconds following inhalation and lasted for no more than 15 seconds. Cough following inhalation in clinical trials was not associated with bronchospasm, exacerbations, deteriorations of disease, or loss of efficacy.

## **6.2 Clinical Trials Experience in Asthma**

In a 6-month randomized, active controlled asthma safety trial, 805 adult patients with moderate to severe persistent asthma were treated with ARCAPTA NEOHALER 300 mcg (n = 268), ARCAPTA NEOHALER 600 mcg (n = 268), and salmeterol (n = 269), all concomitant with inhaled corticosteroids, which were not co-randomized. Of these patients, there were 2 respiratory-related deaths in the ARCAPTA NEOHALER 300-mcg dose group. There were no deaths in the ARCAPTA NEOHALER 600-mcg dose group or in the salmeterol active control group. Serious adverse reactions related to asthma exacerbation were reported for 2 patients in the indacaterol 300-mcg group, 3 patients in the indacaterol 600-mcg group, and no patients in the salmeterol active control group.

In addition, a two-week dose-ranging trial was conducted in 511 adult patients with mild persistent asthma taking inhaled corticosteroids. No deaths, intubations, or serious adverse reactions related to asthma exacerbation were reported in this trial.

## **6.3 Postmarketing Experience**

The following adverse reactions have been identified during worldwide post-approval use of indacaterol, the active ingredient in ARCAPTA NEOHALER. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These adverse reactions are: hypersensitivity reactions, paradoxical bronchospasm, tachycardia/heart rate increase/palpitations, pruritus/rash, and dizziness.

## **7 DRUG INTERACTIONS**

### **7.1 Adrenergic Drugs**

If additional adrenergic drugs are to be administered by any route, they should be used with caution because the sympathetic effects of ARCAPTA NEOHALER may be potentiated [see *Warnings and Precautions* (5.3, 5.6, 5.7, 5.8)].

### **7.2 Xanthine Derivatives, Steroids, or Diuretics**

Concomitant treatment with xanthine derivatives, steroids, or diuretics may potentiate any hypokalemic effect of ARCAPTA NEOHALER [see *Warnings and Precautions* (5.8)].

### **7.3 Non-Potassium Sparing Diuretics**

The ECG changes or hypokalemia that may result from the administration of non-potassium sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical relevance of these effects is not known, caution is advised in the co-administration of ARCAPTA NEOHALER with non-potassium-sparing diuretics.



## **7.4 Monoamine Oxidase Inhibitors, Tricyclic Antidepressants, QTc Prolonging Drugs**

Indacaterol, as with other beta<sub>2</sub>-agonists, should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, or other drugs 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 may have an increased risk of ventricular arrhythmias.

## **7.5 Beta-Blockers**

Beta-adrenergic receptor antagonists (beta-blockers) and ARCAPTA NEOHALER may interfere with the effect of each other when administered concurrently. Beta-blockers not only block the therapeutic effects of beta-agonists, but may produce severe bronchospasm in COPD patients. Therefore, patients with COPD should not normally be treated with beta-blockers. However, under certain circumstances, e.g., as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-blockers in patients with COPD. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

## **7.6 Inhibitors of Cytochrome P450 3A4 and P-gp Efflux Transporter**

Drug interaction studies were carried out using potent and specific inhibitors of CYP3A4 and P-gp (i.e., ketoconazole, erythromycin, verapamil, and ritonavir). The data suggest that systemic clearance is influenced by modulation of both P-gp and CYP3A4 activities and that the 1.9-fold AUC<sub>0-24</sub> increase caused by the strong dual inhibitor ketoconazole reflects the impact of maximal combined inhibition. ARCAPTA NEOHALER was evaluated in clinical trials for up to one year at doses up to 600 mcg. No dose adjustment is warranted at the 75 mcg dose [see *Clinical Pharmacology (12.3)*].

# **8 USE IN SPECIFIC POPULATIONS**

## **8.1 Pregnancy**

### Risk Summary

There are no adequate and well-controlled studies with ARCAPTA NEOHALER in pregnant women. Women should be advised to contact their physician if they become pregnant while taking ARCAPTA NEOHALER.

In animal reproduction studies, there was no evidence of fetal harm or structural abnormalities following subcutaneous administration of indacaterol maleate to pregnant Wistar rats and New Zealand White rabbits during the period of organogenesis at exposures approximately 180 and 410 times the maximum recommended human dose (MRHD of 75 mcg), respectively, on an exposure area under the curve (AUC) basis (see *Data*).

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4%

and 15% to 20%, respectively.

## Clinical Considerations

### *Labor or Delivery*

There are no adequate and well-controlled human studies that have investigated effects of ARCAPTA NEOHALER during labor and delivery. Because beta-agonist may potentially interfere with uterine contractility, ARCAPTA NEOHALER should be used during labor only if the potential benefit justifies the potential risk.

## Data

### *Animal Data*

In embryo-fetal development studies, pregnant Wistar rats received indacaterol maleate, during the period of organogenesis from Gestation Days 6 to 17, at exposures up to 180 times the MRHD (on an AUC basis with maternal subcutaneous doses up to 1 mg/kg/day) and pregnant New Zealand White rabbits received indacaterol maleate, during the period of organogenesis from Gestation Days 7 to 20, at exposures up to 1000 times the MRHD (on an AUC basis with maternal subcutaneous doses up to 3 mg/kg/day). Indacaterol maleate produced no evidence of fetal harm or structural abnormalities in rats and rabbits at exposures up to 180 and 410 times, respectively, the MRHD. Rabbit fetuses were observed with increased incidences of full supernumerary rib, a structural variation at an exposure approximately 1000 times the MRHD.

In a pre- and postnatal development study, pregnant Wistar rats received indacaterol maleate, throughout the period of organogenesis and lactation from Gestation Day 6 through Lactation Day 20, at doses up to 130 times the MRHD (on a mg/m<sup>2</sup> basis with maternal subcutaneous doses up to 1 mg/kg/day). F1 pups received subcutaneous doses of indacaterol maleate up to 1 mg/kg/day from postpartum Days 4 through 20. There was no evidence of maternal toxicity with doses up to 130 times the MRHD. There were no effects on the physical or behavioral development of F1 pups with doses up to 40 times the MRHD (on a mg/m<sup>2</sup> basis with maternal and F1 pup subcutaneous doses up to 0.3 mg/kg/day). There was a decrease in the number of F1 pregnant animals at a dose approximately 130 times the MRHD (on a mg/m<sup>2</sup> basis with maternal and F1 pup subcutaneous doses of 1 mg/kg/day); however, there were no effects on mating or other parameters of reproductive performance.

## **8.2 Lactation**

### Risk Summary

There is no data on the presence of indacaterol in human milk, effect on the breastfed infant, or the effects on milk production. Indacaterol is present in the milk of lactating rats (*see Data*). The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ARCAPTA NEOHALER and any potential adverse effects on the breastfed child from ARCAPTA NEOHALER or from the underlying maternal condition.

## Data

### *Animal Data*

Indacaterol and its metabolites were detected in the milk within 1 hour following a single

subcutaneous dose of 650 mcg radiolabeled indacaterol maleate administered to lactating rats postpartum Days 8 and 9.

#### **8.4 Pediatric Use**

The safety and effectiveness of ARCAPTA NEOHALER in pediatric patients have not been established. ARCAPTA NEOHALER is not indicated for use in pediatric patients.

#### **8.5 Geriatric Use**

Based on available data, no adjustment of ARCAPTA NEOHALER dosage in geriatric patients is warranted. Of the total number of patients who received ARCAPTA NEOHALER at the recommended dosage of 75 mcg once daily in the clinical studies from the pooled 3-month database, 153 were 65 to 74 years, and 57 were  $\geq$  75 years of age.

No overall differences in effectiveness were observed, and in the 3-month pooled data, the adverse drug reaction profile was similar in the older population compared to the patient population overall.

#### **8.6 Hepatic Impairment**

Patients with mild and moderate hepatic impairment showed no relevant changes in  $C_{max}$  or AUC, nor did protein binding differ between mild and moderate hepatically impaired subjects and their healthy controls. Studies in subjects with severe hepatic impairment were not performed.

#### **8.7 Renal Impairment**

Due to the very low contribution of the urinary pathway to total body elimination, a study in renally impaired subjects was not performed.

### **10 OVERDOSAGE**

In COPD patients, single doses of 40 times the 75 mcg dose were associated with moderate increases in pulse rate, systolic blood pressure and QTc interval.

The expected signs and symptoms associated with overdosage of ARCAPTA NEOHALER are those of excessive beta-adrenergic stimulation and occurrence or exaggeration of any of the signs and symptoms, e.g., angina, hypertension or hypotension, tachycardia, with rates up to 200 beats per minute, arrhythmias, nervousness, headache, tremor, dry mouth, palpitation, muscle cramps, nausea, dizziness, fatigue, malaise, hypokalemia, hyperglycemia, metabolic acidosis, and insomnia. As with all inhaled sympathomimetic medications, cardiac arrest and even death may be associated with an overdose of ARCAPTA NEOHALER.

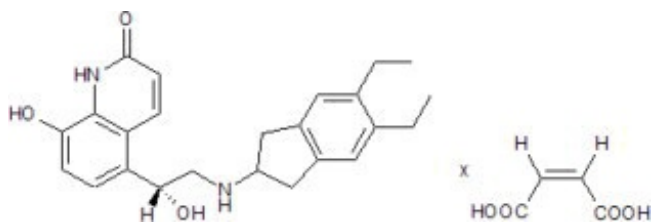
Treatment of overdosage consists of discontinuation of ARCAPTA NEOHALER together with institution of appropriate symptomatic and supportive therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medication can produce bronchospasm. There is insufficient evidence to determine if dialysis is beneficial for overdosage of ARCAPTA NEOHALER. Cardiac monitoring is recommended in cases of overdosage.

## 11 DESCRIPTION

ARCAPTA NEOHALER consists of a dry powder formulation of indacaterol maleate for oral inhalation only with the NEOHALER inhaler. The inhalation powder is packaged in clear gelatin capsules.

Each clear, hard gelatin capsule contains a dry powder blend of 75 mcg of indacaterol (equivalent to 97 mcg of indacaterol maleate) with approximately 25 mg of lactose monohydrate (which contains trace levels of milk protein) as the carrier.

The active component of ARCAPTA NEOHALER is indacaterol maleate, a (R) enantiomer. Indacaterol maleate is a selective beta<sub>2</sub>-adrenergic agonist. Its chemical name is (R)-5-[2-(5,6-Diethylindan-2-ylamino)-1-hydroxyethyl]-8-hydroxy-1H-quinolin-2-one maleate; its structural formula is



Indacaterol maleate has a molecular weight of 508.56 g/mol, and its empirical formula is C<sub>24</sub>H<sub>28</sub>N<sub>2</sub>O<sub>3</sub>•C<sub>4</sub>H<sub>4</sub>O<sub>4</sub>. Indacaterol maleate is a white to very slightly grayish or very slightly yellowish powder. Indacaterol maleate is freely soluble in N-methylpyrrolidone and dimethylformamide, slightly soluble in methanol, ethanol, propylene glycol and polyethylene glycol 400, very slightly soluble in water, isopropyl alcohol and practically insoluble in 0.9% sodium chloride in water, ethyl acetate and n-octanol.

The NEOHALER inhaler is a plastic device used for inhaling ARCAPTA. The amount of drug delivered to the lung will depend on patient factors, such as inspiratory flow rate and inspiratory time. Under standardized *in vitro* testing at a fixed flow rate of 60 L/min for 2 seconds, the NEOHALER inhaler delivered 57 mcg for the 75 mcg dose strength (equivalent to 73.9 mcg of indacaterol maleate) from the mouthpiece. Peak inspiratory flow rates (PIFR) achievable through the NEOHALER inhaler were evaluated in 26 adult patients with COPD of varying severity. Mean PIFR was 95 L/min (range 52-133 L/min) for adult patients. Approximately ninety-five percent of the population studied generated a PIFR through the device exceeding 60 L/min.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Indacaterol is a (LABA).

When inhaled, indacaterol acts locally in the lung as a bronchodilator. *In vitro* studies have shown that indacaterol has more than 24-fold greater agonist activity at beta<sub>2</sub>-receptors compared to beta<sub>1</sub>-receptors and 20-fold greater agonist activity compared to beta<sub>3</sub>-receptors. This selectivity profile is similar to formoterol. The clinical significance of these findings is unknown. Although beta<sub>2</sub>-receptors are the predominant adrenergic receptors in bronchial smooth muscle and beta<sub>1</sub>-receptors are the predominant receptors in the heart, there are also beta<sub>2</sub>-adrenergic receptors in the human heart comprising 10% to 50% of the total adrenergic receptors. The precise function of these

receptors is not known, but their presence raises the possibility that even highly selective beta<sub>2</sub>-adrenergic agonists may have cardiac effects.

The pharmacological effects of beta<sub>2</sub>-adrenoceptor agonist drugs, including indacaterol, are at least in part attributable to stimulation of intracellular adenyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate to cyclic-3', 5'-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially mast cells.

## **12.2 Pharmacodynamics**

### Systemic Safety

The major adverse effects of inhaled beta<sub>2</sub>-adrenergic agonists occur as a result of excessive activation of systemic beta-adrenergic receptors. The most common adverse effects in adults include skeletal muscle tremor and cramps, insomnia, tachycardia, decreases in serum potassium and increases in plasma glucose.

Changes in serum potassium and plasma glucose were evaluated in COPD patients in double-blind studies. In pooled data, at the recommended 75 mcg dose, at 1 hour post-dose at Week 12, there was no change compared to placebo in serum potassium, and change in mean plasma glucose was 0.07 mmol/L.

### Cardiac Electrophysiology

The effect of ARCAPTA NEOHALER on the QT interval was evaluated in a double-blind, placebo- and active (moxifloxacin)-controlled study following multiple doses of indacaterol 150 mcg, 300 mcg, or 600 mcg once-daily for 2 weeks in 404 healthy volunteers. Fridericia's method for heart rate correction was employed to derive the corrected QT interval (QTcF). Maximum mean prolongation of QTcF intervals were < 5 ms, and the upper limit of the 90% CI was below 10 ms for all time-matched comparisons vs. placebo. There was no evidence of a clinically relevant concentration-delta QTc relationship in the range of doses evaluated.

The effect of 150 mcg and 300 mcg once daily of ARCAPTA NEOHALER on heart rate and rhythm was assessed using continuous 24-hour ECG recording (Holter monitoring) in a subset of 605 patients with COPD from a 26-week, double-blind, placebo-controlled study. Holter monitoring occurred once at baseline and up to 3 times during the 26-week treatment period (at Weeks 2, 12 and 26). A comparison of the mean heart rate over 24 hours showed no increase from baseline. The hourly heart rate analysis was similar compared to placebo. The pattern of diurnal variation over 24 hours was maintained and was similar to placebo. No difference from placebo was seen in the rates of atrial fibrillation, time spent in atrial fibrillation and also the maximum ventricular rate of atrial fibrillation. No clear patterns in the rates of single ectopic beats, couplets or runs were seen across visits. Because the summary data on rates of ventricular ectopic beats can be difficult to interpret, specific pro-arrhythmic criteria were analyzed. In this analysis, baseline occurrence of ventricular ectopic beats was compared to change from baseline, setting certain parameters for the change to describe the pro-arrhythmic response. The number of patients with a documented pro-arrhythmic response was very similar compared to placebo. Overall, there was no clinically relevant difference in the development of arrhythmic events in patients receiving indacaterol treatment over those patients who received placebo.

## Tachyphylaxis/Tolerance

Tolerance to the effects of inhaled beta-agonists can occur with regularly scheduled, chronic use. In two 12-week clinical efficacy trials in 323 and 318 adult patients with COPD, ARCAPTA NEOHALER improvement in lung function (as measured by the FEV<sub>1</sub>) observed at Week 4 with ARCAPTA NEOHALER was consistently maintained over the 12-week treatment period in both trials.

## **12.3 Pharmacokinetics**

### Absorption

The median time to reach peak serum concentrations of indacaterol was approximately 15 minutes after single or repeated inhaled doses. Systemic exposure to indacaterol increased with increasing dose (150 mcg to 600 mcg) in a dose proportional manner, and was about dose-proportional in the dose range of 75 mcg to 150 mcg. Absolute bioavailability of indacaterol after an inhaled dose was on average 43% to 45%. Systemic exposure results from a composite of pulmonary and intestinal absorption.

Indacaterol serum concentrations increased with repeated once-daily administration. Steady-state was achieved within 12 to 15 days. The mean accumulation ratio of indacaterol, i.e., AUC over the 24-hour dosing interval on Day 14 or Day 15 compared to Day 1, was in the range of 2.9 to 3.8 for once-daily inhaled doses between 75 mcg and 600 mcg.

### Distribution

After intravenous infusion the volume of distribution (V<sub>z</sub>) of indacaterol was 2361 L to 2557 L indicating an extensive distribution. The *in vitro* human serum and plasma protein binding was 94.1% to 95.3% and 95.1% to 96.2%, respectively.

### Elimination

In clinical studies which included urine collection the amount of indacaterol excreted unchanged *via* urine was generally lower than 2% of the dose. Renal clearance of indacaterol was, on average, between 0.46 L/h and 1.2 L/h. When compared with the serum clearance of indacaterol of 18.8 L/h to 23.3 L/h, it is evident that renal clearance plays a minor role (about 2% to 6% of systemic clearance) in the elimination of systemically available indacaterol.

In a human absorption, distribution, metabolism, excretion (ADME) study where indacaterol was given orally, the fecal route of excretion was dominant over the urinary route. Indacaterol was excreted into human feces primarily as unchanged parent drug (54% of the dose) and, to a lesser extent, hydroxylated indacaterol metabolites (23% of the dose). Mass balance was complete with  $\geq 90\%$  of the dose recovered in the excreta.

Indacaterol serum concentrations declined in a multi-phasic manner with an average terminal half-life ranging from 45.5 to 126 hours. The effective half-life, calculated from the accumulation of indacaterol after repeated dosing with once-daily doses between 75 mcg and 600 mcg ranged from 40 to 56 hours which is consistent with the observed time-to-steady state of approximately 12 to 15 days.

### *Metabolism*

After oral administration of radiolabeled indacaterol in the human ADME study unchanged indacaterol was the main component in serum, accounting for about one

third of total drug-related AUC over 24 hours. A hydroxylated derivative was the most prominent metabolite in serum. Phenolic O-glucuronides of indacaterol and hydroxylated indacaterol were further prominent metabolites. A diastereomer of the hydroxylated derivative, a N-glucuronide of indacaterol, and C- and N-dealkylated products were further metabolites identified.

*In vitro* investigations indicated that UGT1A1 was the only UGT isoform that metabolized indacaterol to the phenolic O-glucuronide. The oxidative metabolites were found in incubations with recombinant CYP1A1, CYP2D6, and CYP3A4. CYP3A4 is concluded to be the predominant isoenzyme responsible for hydroxylation of indacaterol.

*In vitro* investigations indicated that indacaterol is a low affinity substrate for the efflux pump P-gp.

*In vitro* investigations indicated that indacaterol has negligible potential to cause metabolic interactions with medications (by inhibition or induction of cytochrome P450 enzymes, or induction of UGT1A1) at the systemic exposure levels achieved in clinical practice. *In vitro* investigation furthermore indicated that, *in vivo*, indacaterol is unlikely to significantly inhibit transporter proteins, such as P-gp, MRP2, BCRP, the cationic substrate transporters hOCT1 and hOCT2, and the human multidrug and toxin extrusion transporters hMATE1 and hMATE2K, and that indacaterol has negligible potential to induce P-gp or MRP2.

### Specific Populations

A population pharmacokinetic analysis was performed for indacaterol utilizing data from 3 controlled clinical trials that included 1,844 patients with COPD aged 40 to 88 years who received treatment with ARCAPTA NEOHALER.

The population analysis showed that no dose adjustment is warranted based on the effect of age, gender and weight on systemic exposure in COPD patients after inhalation of ARCAPTA NEOHALER. The population pharmacokinetic analysis did not suggest any difference between ethnic subgroups in this population.

### *Patients With Hepatic Impairment*

Patients with mild and moderate hepatic impairment showed no relevant changes in  $C_{max}$  or AUC of indacaterol, nor did protein binding differ between mild and moderate hepatically impaired subjects and their healthy controls. Studies in subjects with severe hepatic impairment were not performed.

### *Patients With Renal Impairment*

Due to the very low contribution of the urinary pathway to total body elimination, a study in renally impaired subjects was not performed.

### Drug Interaction Studies

Drug interaction studies were carried out using potent and specific inhibitors of CYP3A4 and P-gp (i.e., ketoconazole, erythromycin, verapamil and ritonavir).

Verapamil: Coadministration of indacaterol 300 mcg (single dose) with verapamil (80 mg three times daily for 4 days) showed 2-fold increase in indacaterol AUC<sub>0-24</sub>, and 1.5-fold increase in indacaterol  $C_{max}$ .

Erythromycin: Coadministration of indacaterol inhalation powder 300 mcg (single dose) with erythromycin (400 mg four times daily for 7 days) showed a 1.4-fold increase in

indacaterol AUC<sub>0-24</sub>, and 1.2-fold increase in indacaterol C<sub>max</sub>.

Ketoconazole: Coadministration of indacaterol inhalation powder 300 mcg (single dose) with ketoconazole (200 mg twice daily for 7 days) caused a 1.9-fold increase in indacaterol AUC<sub>0-24</sub>, and 1.3-fold increase in indacaterol C<sub>max</sub>.

Ritonavir: Coadministration of indacaterol 300 mcg (single dose) with ritonavir (300 mg twice daily for 7.5 days) resulted in a 1.7-fold increase in indacaterol AUC<sub>0-24</sub> whereas indacaterol C<sub>max</sub> was unaffected [see *Drug Interactions (7.6)*].

## 12.5 Pharmacogenomics

The pharmacokinetics of indacaterol were prospectively investigated in subjects with the *UGT1A1* (TA)<sub>7</sub>/(TA)<sub>7</sub> genotype (low *UGT1A1* expression; also referred to as \*28) and the (TA)<sub>6</sub>, (TA)<sub>6</sub> genotype. Steady-state AUC and C<sub>max</sub> of indacaterol were 1.2-fold higher in the [(TA)<sub>7</sub>, (TA)<sub>7</sub>] genotype, suggesting no relevant effect of *UGT1A1* genotype of indacaterol exposure.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies were conducted in rats using inhalation administration and transgenic mice using oral administration to evaluate the carcinogenic potential of indacaterol maleate.

Indacaterol produced no treatment-related increases in the incidence of tumors in a 2-year inhalation study in Wistar rats at inhaled doses up to 2.09 mg/kg/day (approximately 270 times the MRHD on a mg/m<sup>2</sup> basis). A 26-week oral (gavage) study in CB6F1/TgrasH2 hemizygous mice with indacaterol at doses up to 600 mg/kg/day did not show any evidence of tumorigenicity.

Indacaterol tested negative in the following genotoxicity assays: the *in vitro* Ames test, *in vitro* chromosomal aberration test in V79 Chinese hamster cells, and *in vivo* bone marrow micronucleus test in rats.

Indacaterol had no effects on fertility and reproductive performance in male and female rats at subcutaneous doses up to 2 mg/kg/day (approximately 260 times the MRDH on a mg/m<sup>2</sup> basis).

## 14 CLINICAL STUDIES

The ARCAPTA NEOHALER COPD clinical development program included three dose-ranging trials and six confirmatory trials (Trial 3, a 26-week seamless adaptive design trial that included an initial 2 week dose ranging phase; Trials 4, 5, and 6, 12-week trials; Trial 7, a 26-week trial; and Trial 8, a 52-week trial).

### Dose-Ranging Trials

Dose selection for ARCAPTA NEOHALER for COPD was based on three dose-ranging trials (Trial 1, a 2-week dose-ranging trial in an asthma population; Trial 2, a 2-week dose-ranging trial in a COPD population; and Trial 3, a 26-week adaptive seamless design trial that included an initial 2-week dose ranging phase). Although ARCAPTA NEOHALER



is not indicated for asthma, dose selection was primarily based upon the results from the dose-ranging trial in asthma patients (Trial 1) as an asthma population is the most responsive to beta-agonist bronchodilation and is most likely to demonstrate a dose response. Dose-ranging in COPD patients (Trials 2 and 3) provided supportive information.

### Dose-Ranging in Asthma

#### **ARCAPTA NEOHALER is not indicated for asthma.**

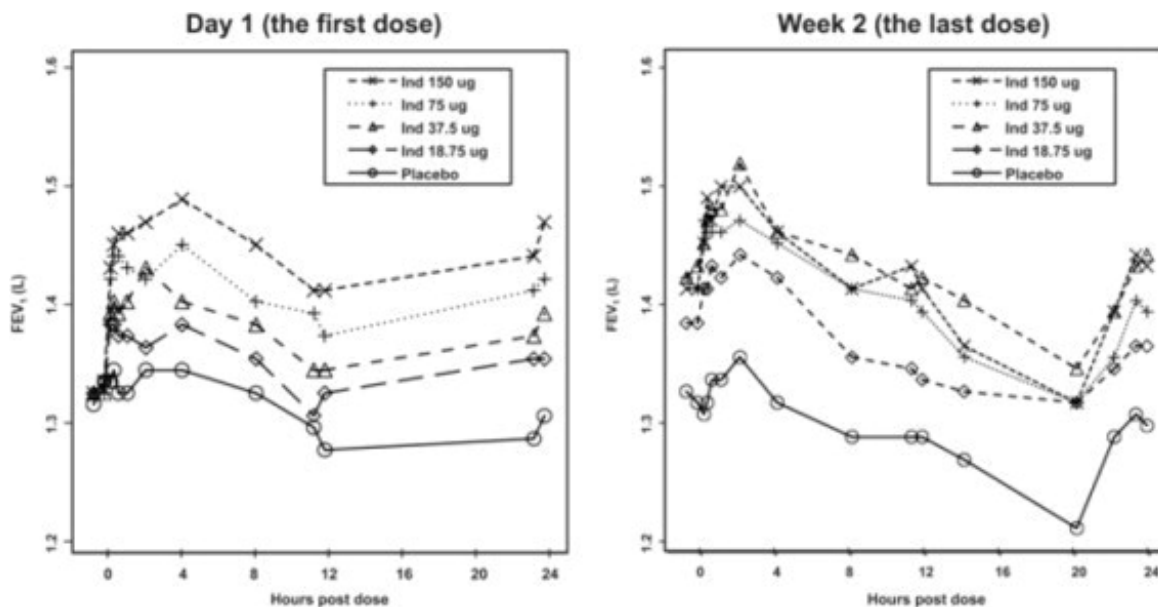
Trial 1 was a 2-week, randomized, double-blinded, placebo-controlled design that enrolled 511 patients with persistent asthma 18 years of age and older. All enrolled patients were required to be taking inhaled corticosteroids, had an FEV<sub>1</sub> of  $\geq 50\%$  and  $\leq 90\%$  predicted, and FEV<sub>1</sub> reversibility after albuterol of at least 12% and at least 200 mL. Trial 1 included ARCAPTA NEOHALER doses of 18.75, 37.5, 75, and 150 mcg once daily, a salmeterol active control group, and placebo. The trial showed that the effect on FEV<sub>1</sub> in patients treated with ARCAPTA NEOHALER 18.75 and 37.5 mcg doses was lower compared to patients treated with other ARCAPTA NEOHALER doses, particularly after the first dose. The effect did not clearly differ between the 75 mcg and 150 mcg doses.

Results of the ARCAPTA NEOHALER and placebo treatment arms are as follows. After the first dose (Day 1), the peak (4 hour) FEV<sub>1</sub> was 2.58L in the placebo group, with a treatment difference of 0.04L (95% CI -0.01, 0.09) in the 18.75 mcg ARCAPTA NEOHALER group, 0.04L (-0.01, 0.09) in the 37.5 mcg group, 0.12L (0.07, 0.17) in the 75 mcg group, and 0.15L (0.10, 0.20) in the 150 mcg group. The Day 2 trough FEV<sub>1</sub> was 2.45L in the placebo group, with a treatment difference of 0.02L (95% CI -0.05, 0.08), 0.08L (0.01, 0.15), 0.09L (0.03, 0.16) and 0.16L (0.09, 0.22) in the ARCAPTA NEOHALER groups, respectively. At Day 14, the peak (4 hour) FEV<sub>1</sub> was 2.55L in the placebo group, with a treatment difference of 0.12L (95% CI 0.05, 0.20) in the 18.75 mcg ARCAPTA NEOHALER group, 0.14L (0.06, 0.21) in the 37.5 mcg group, 0.23L (0.15, 0.30) in the 75 mcg group, and 0.20L (0.13, 0.27) in the 150 mcg group. The Day 15 FEV<sub>1</sub> (primary endpoint) was 2.42L in the placebo group, with a treatment difference of 0.09L (95% CI 0.00, 0.17), 0.11L (0.02, 0.19), 0.17L (0.08, 0.26), and 0.12L (0.04, 0.21) in the ARCAPTA NEOHALER groups, respectively.

### Dose-Ranging in COPD

Trial 2 was a 2-week, randomized, double-blinded, placebo-controlled design that enrolled 552 patients with a clinical diagnosis of COPD, who were 40 years or older, had a smoking history of at least 10 pack years, had a post-bronchodilator FEV<sub>1</sub> less than 80% and at least 30% of the predicated normal value and a post-bronchodilator ratio of FEV<sub>1</sub> over forced vital capacity (FEV<sub>1</sub>/FVC) of less than 70%. Trial 2 included ARCAPTA NEOHALER doses of 18.75, 37.5, 75 and 150 mcg once daily, a salmeterol active control group, and placebo. Results of the ARCAPTA NEOHALER and placebo arms are shown in Figure 1. The trial showed that the effect on FEV<sub>1</sub> in patients treated with ARCAPTA NEOHALER 18.75 mcg dose was lower compared to patients treated with other ARCAPTA NEOHALER doses. Although a dose-response relationship was observed at Day 1, the effect did not clearly differ among the 37.5, 75 and 150 mcg doses by Day 15.

#### **Figure 1: LS Mean FEV<sub>1</sub> Time Profile Curve Over 24 Hours After ARCAPTA NEOHALER Day 1 and Week 2 in Trial 2 (COPD Dose Ranging)**



The 2-week dose ranging phase of Trial 3 included ARCAPTA NEOHALER doses of 75 mcg, 150 mcg, 300 mcg, and 600 mcg once daily, placebo, and two active comparators. Although a dose-response relationship was observed at Week 2, the effect did not clearly differ among the ARCAPTA NEOHALER doses.

### Confirmatory Trials

The ARCAPTA NEOHALER COPD development program included six confirmatory trials that were randomized, double-blinded placebo and active-controlled in design (Trial 3, a 26-week seamless adaptive design trial that included an initial 2-week dose-ranging phase; Trials 4, 5, and 6, 12-week trials; Trial 7, a 26-week trial; and Trial 8, a 52-week trial). After the initial 2-week dose-ranging portion of the design, Trial 3 was conducted with ARCAPTA NEOHALER doses of 150 mcg and 300 mcg once daily, placebo, and an active comparator. Trials 4 and 5 were conducted with ARCAPTA NEOHALER dose of 75 mcg once daily, and placebo. Trial 6 was conducted with ARCAPTA NEOHALER dose of 150 mcg once daily and placebo. Trial 7 was conducted with ARCAPTA NEOHALER dose of 150 mcg once daily, an active comparator, and placebo. Trial 8 was conducted with ARCAPTA NEOHALER doses of 300 mcg and 600 mcg once daily, an active comparator, and placebo.

As Trials 3, 6, 7, and 8 were conducted with doses of ARCAPTA NEOHALER higher than 75 mcg, the results of Trials 4 and 5, which included ARCAPTA NEOHALER 75 mcg, are the focus of this section.

These six trials enrolled 5474 patients with a clinical diagnosis of COPD, who were 40 years or older, had a smoking history of at least 10 pack years, had a post-bronchodilator FEV<sub>1</sub> less than 80% and at least 30% of the predicted normal value and a post-bronchodilator ratio of FEV<sub>1</sub> over FVC of less than 70%.

Assessment of efficacy in these six COPD trials was based on FEV<sub>1</sub>. The primary efficacy endpoint was 24-hour post-dose trough FEV<sub>1</sub> (defined as the average of two FEV<sub>1</sub> measurements taken after 23 hours 10 minutes and 23 hours and 45 minutes after the previous dose) after 12 weeks of treatment in all 6 trials. Other efficacy variables included other FEV<sub>1</sub> and FVC time points, rescue medication use, symptoms, and health-related quality of life measured using the St. George's Respiratory

Questionnaire (SGRQ).

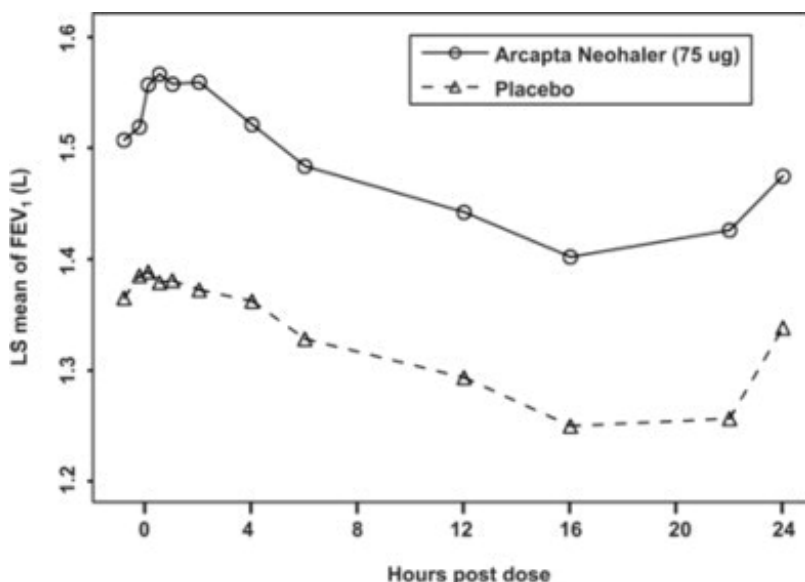
In all six confirmatory COPD trials, all doses of ARCAPTA NEOHALER tested (75 mcg, 150 mcg, 300 mcg, and 600 mcg) showed significantly greater 24-hour post-dose trough FEV<sub>1</sub> compared to placebo at 12 weeks. Results of Trials 4 and 5, which compared ARCAPTA NEOHALER at the dose of 75 mcg once daily to placebo are shown in Table 2.

**Table 2: Least Squares Mean for Trough FEV<sub>1</sub> at 12 Weeks**

<b>Treatment</b>	<b>Trough FEV<sub>1</sub> at Week 12 (liters)</b>	<b>Treatment Difference Least Squares Mean (95% CI)</b>
<b>Trial 4 (N = 323)</b>		
Indacaterol 75 mcg	1.38	0.12 (0.08, 0.15)
Placebo	1.26	
<b>Trial 5 (N = 318)</b>		
Indacaterol 75 mcg	1.49	0.14 (0.10, 0.18)
Placebo	1.35	

In addition, serial FEV<sub>1</sub> measurements in patients treated with ARCAPTA NEOHALER demonstrated a bronchodilatory treatment effect after the first dose compared to placebo at 5 minutes post dose of 0.09 L (Trial 4) and 0.10 L (Trial 5). The mean peak improvement relative to baseline within the first 4 hours after the first dose (Day 1) was 0.19 L (Trial 4) and 0.22 L (Trial 5) and was 0.24 L (Trial 4) and 0.27 L (Trial 5) after 12 weeks. Improvement in lung function observed at Week 4 was consistently maintained over the 12-week treatment period in both trials. In Trial 5, 24-hour spirometry was assessed in a subset of 239 patients. See Figure 2.

**Figure 2: Least Squares Mean FEV<sub>1</sub> Time Profile Curve Over 24 Hours at Week 12 in Trial 5**



In both COPD clinical trials, including the 75 mcg dose (Trials 4 and 5), patients treated with ARCAPTA NEOHALER used less daily rescue albuterol during the trial compared to patients treated with placebo.

Health-related quality of life was measured using the SGRQ in all six confirmatory COPD clinical trials. SGRQ is a disease-specific patient reported instrument which measures symptoms, activities, and its impact on daily life. At Week 12, pooled data from these trials demonstrated an improvement over placebo in SGRQ total score of -3.8 with a 95% CI of (-5.3, -2.3) for the ARCAPTA NEOHALER 75 mcg dose, -4.6 with a 95% CI of (-5.5, -3.6) for 150 mcg, and -3.8 with a 95% CI of (-4.9, -2.8) for 300 mcg. The CI for this change are widely overlapping with no dose ordering. Results from individual studies were variable, but are generally consistent with the pooled data results.

## **16 HOW SUPPLIED/STORAGE AND HANDLING**

### How Supplied

ARCAPTA NEOHALER (indacaterol) inhalation powder:

- contains 75 mcg indacaterol inhalation powder per capsule
- packaged in aluminum blister cards
- unit Dose (blister pack), Box of 30 (5 blister cards with 6 capsules each) NDC 63402-675-30
- NEOHALER inhaler consists of a white protective cap and a base with mouthpiece, capsule chamber and two translucent red push buttons

### Storage and Handling

- Store in a dry place at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].
- Protect capsule from light and moisture.
- ARCAPTA capsules should be used with the NEOHALER inhaler only. The NEOHALER inhaler should not be used with any other capsules.
- Capsules should always be stored in the blister and only removed from the blister immediately before use.
- Always use the new NEOHALER inhaler provided with each new prescription.
- Keep out of the reach of children.

## **17 PATIENT COUNSELING INFORMATION**

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use)

### Serious Asthma-Related Events

Patients should be informed that LABA, such as ARCAPTA NEOHALER, when used as monotherapy [without an inhaled corticosteroid], increase the risk of serious asthma-related events, including asthma-related death. ARCAPTA NEOHALER is not indicated for the treatment of asthma [see *Warnings and Precautions (5.1)*].

### Instructions for Administering ARCAPTA NEOHALER

It is important for patients to understand how to correctly administer ARCAPTA capsules using the NEOHALER device [see *Instructions for Use*]. Patients should be instructed

that ARCAPTA capsules should only be administered via the NEOHALER device and the NEOHALER device should not be used for administering other medications. The contents of ARCAPTA capsules are for oral inhalation only and must not be swallowed.

ARCAPTA capsules should always be stored in sealed blisters. Only one ARCAPTA capsule should be removed immediately before use, or its effectiveness may be reduced. Additional ARCAPTA capsules that are exposed to air (i.e., not intended for immediate use) should be discarded.

#### Not for Acute Symptoms

ARCAPTA NEOHALER is not meant to relieve acute symptoms or exacerbations of COPD and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, SABA, such as albuterol. The healthcare provider should provide the patient with such medication and instruct the patient in how it should be used.

Patients should be instructed to notify their healthcare provider immediately if they experience any of the following:

- worsening of symptoms
- decreasing effectiveness of inhaled, SABAs
- need for more inhalations than usual of inhaled, SABAs
- significant decrease in lung function as outlined by their healthcare provider.

Patients should not stop therapy with ARCAPTA NEOHALER without physician/healthcare provider guidance since symptoms may recur after discontinuation.

#### Do Not Use Additional Long-Acting Beta<sub>2</sub>-Agonists

Patients who have been taking inhaled, SABAs on a regular basis should be instructed to discontinue the regular use of these products and use them only for the symptomatic relief of acute symptoms [*see Warnings and Precautions (5.2)*].

When patients are prescribed ARCAPTA NEOHALER, other inhaled medications containing LABAs should not be used. Patients should not use more than the recommended once daily dose of ARCAPTA NEOHALER. Excessive use of sympathomimetics may cause significant cardiovascular effects, and may be fatal [*see Warnings and Precautions (5.3)*].

#### Risks Associated With Beta-Agonist Therapy

Patients should be informed of adverse effects associated with beta<sub>2</sub>-agonists, such as palpitations, chest pain, rapid heart rate, tremor, or nervousness.

Manufactured by:

Novartis Pharmaceuticals Corporation

East Hanover, New Jersey 07936

T2021-106

**PATIENT INFORMATION**  
**ARCAPTA® (ar-CAP-ta) NEOHALER®**  
**(indacaterol inhalation powder)**

**Important: Do not swallow ARCAPTA capsules. ARCAPTA capsules are used**

**only with the NEOHALER inhaler that comes with ARCAPTA NEOHALER. Do not place a capsule in the mouthpiece of the NEOHALER inhaler.**

**What is ARCAPTA NEOHALER?**

- ARCAPTA NEOHALER is a long-acting beta<sub>2</sub>-adrenergic agonist (LABA) used to control the symptoms of chronic obstructive pulmonary disease (COPD) in adults with COPD. COPD is a chronic lung disease that includes chronic bronchitis, emphysema, or both. LABA medicines, such as ARCAPTA NEOHALER help the muscles around the airways in your lungs stay relaxed to prevent symptoms, such as wheezing, cough, chest tightness and shortness of breath.
- ARCAPTA NEOHALER is for long-term use and should be taken 1 time each day, to improve the symptoms of COPD for better breathing.
- **ARCAPTA NEOHALER is not used to treat sudden symptoms of COPD.** Always have a short-acting beta<sub>2</sub>-agonist medicine (rescue inhaler) with you to treat sudden symptoms of COPD. If you do not have a rescue inhaler, contact your healthcare provider to have one prescribed for you.
- **ARCAPTA NEOHALER is not for the treatment of asthma.** It is not known if ARCAPTA NEOHALER is safe and effective in people with asthma.
- **ARCAPTA NEOHALER should not be used in children.** It is not known if ARCAPTA NEOHALER is safe and effective in children.

**Do not use ARCAPTA NEOHALER if you:**

- have asthma.
- are allergic to indacaterol or any of the ingredients in ARCAPTA NEOHALER. Ask your healthcare provider if you are not sure. See **“What are the ingredients in ARCAPTA NEOHALER?”** at the end of this Patient Information leaflet for a complete list of ingredients in ARCAPTA NEOHALER.

**Before using ARCAPTA NEOHALER, tell your healthcare provider about all of your medical conditions, including if you:**

- have heart problems.
- have high blood pressure.
- have seizures.
- have thyroid problems.
- have diabetes.
- are pregnant or plan to become pregnant. It is not known if ARCAPTA NEOHALER can harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if the medicine indacaterol in ARCAPTA NEOHALER passes into your breast milk and if it can harm your baby. You and your healthcare provider should decide if you will take ARCAPTA or breastfeed.
- are allergic to any of the ingredients in ARCAPTA NEOHALER, any other medicines, or food products.

ARCAPTA NEOHALER contains lactose (milk sugar) and a small amount of milk proteins. It is possible that allergic reactions may happen in patients who have a severe milk protein allergy.

**Tell your healthcare provider about all the medicines you take,** including prescription and over-the-counter medicines, vitamins, and herbal supplements. ARCAPTA NEOHALER and certain other medicines may interact with each other. This may cause serious side effects.

Know the medicines you take. Keep a list of your medicines with you to show your healthcare provider and pharmacist each time you get a new medicine.

### **How should I use ARCAPTA NEOHALER?**

**Read the step-by-step instructions for using ARCAPTA NEOHALER at the end of this Patient Information leaflet.**

- **Do not** use ARCAPTA NEOHALER unless your healthcare provider has taught you how to use the inhaler and you understand how to use it correctly. Ask your healthcare provider or pharmacist if you have any questions.
- Use ARCAPTA NEOHALER exactly as prescribed. **Do not use ARCAPTA NEOHALER more often than prescribed.**
- **Use 1 ARCAPTA capsule inhaled through the NEOHALER inhaler 1 time each day**, at the same time of the day.
- If you miss a dose of ARCAPTA NEOHALER, take it as soon as you remember. Do not take more than 1 dose in 24 hours.
- **Do not swallow ARCAPTA capsules.** ARCAPTA capsules are for oral inhalation use only.
- Only use ARCAPTA capsules with the NEOHALER inhaler.
- ARCAPTA capsules should always be stored in the sealed blisters and removed immediately before use. Throw away (discard) any ARCAPTA capsules that are removed from the blister and not used immediately.
- Always use the new NEOHALER inhaler that is provided with each new prescription.
- **ARCAPTA NEOHALER does not relieve sudden symptoms of COPD.** Always have a rescue inhaler medicine with you to treat sudden symptoms. If you do not have a rescue inhaler medicine, call your healthcare provider to have one prescribed for you.
- **Do not** stop using ARCAPTA NEOHALER or other medicines to control or treat your COPD unless told to do so by your healthcare provider because your symptoms might get worse. Your healthcare provider will change your medicines as needed.
- **Call your healthcare provider or get emergency medical care right away** if your breathing problems worsen with ARCAPTA NEOHALER, you need to use your rescue medicine more often than usual, or your rescue inhaler medicine does not work as well for you at relieving your symptoms.

### **What are the possible side effects with ARCAPTA NEOHALER?**

**ARCAPTA NEOHALER can cause serious side effects, including:**

- **People with asthma who take LABA medicines, such as ARCAPTA NEOHALER, without also using medicine called an inhaled corticosteroid, have an increased risk of serious problems from asthma, including being hospitalized, needing a tube placed in their airway to help them breathe, or death.**
  - **Call your healthcare provider if breathing problems worsen over time while using ARCAPTA NEOHALER.** You may need a different treatment.
  - **Get emergency medical care if:**
    - breathing problems worsen quickly.
    - you use your rescue inhaler medicine, but it does not relieve your breathing problems.
- **COPD symptoms that get worse over time.** If your COPD symptoms worsen over time, do not increase your dose of ARCAPTA NEOHALER, instead call your

healthcare provider.

- **Using too much of a LABA medicine may cause:**

- chest pain
- fast and irregular heartbeat
- tremor
- increased blood pressure
- headache
- nervousness

- **Serious allergic reactions.** Stop using ARCAPTA NEOHALER and call your healthcare provider or get emergency medical care right away if you get any of the following symptoms of a serious allergic reaction.

- rash
- swelling of the tongue, lips, and face
- hives
- difficulty breathing or swallowing

- **Sudden shortness of breath can happen immediately after using ARCAPTA NEOHALER.** Sudden shortness of breath may be life-threatening. If you have sudden breathing problems immediately after inhaling your medicine, call your healthcare provider or go to the nearest hospital emergency room right away.

- **Effects on your heart:**

- fast or irregular heartbeat, awareness of a heartbeat
- increased blood pressure
- chest pain

- **Changes in laboratory blood levels,** including high levels of blood sugar (hyperglycemia) and low levels of potassium (hypokalemia), which may cause symptoms of muscle spasm, muscle weakness or abnormal heart rhythm.

**Common side effects of ARCAPTA NEOHALER include:** runny nose, cough, sore throat, headache and nausea.

Tell your healthcare provider about any side effect that bothers you or that does not go away.

These are not all the possible side effects of ARCAPTA NEOHALER. For more information, ask your healthcare provider or pharmacist.

**Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.**

#### **How should I store ARCAPTA NEOHALER?**

- Store ARCAPTA NEOHALER (inhaler and blister-packaged capsules) at room temperature between 59°F to 86°F (15°C to 30°C).
- Store ARCAPTA NEOHALER in a dry place.
- Protect ARCAPTA capsules from light and moisture.
- **Do not** remove ARCAPTA capsules from their foil package until just before use.
- **Do not** store ARCAPTA capsules in the NEOHALER inhaler.
- **Keep ARCAPTA NEOHALER and all medicines out of the reach of children.**

#### **General Information about the safe and effective use of ARCAPTA NEOHALER.**

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use ARCAPTA NEOHALER for a condition for which it was not



prescribed. Do not give ARCAPTA NEOHALER to other people, even if they have the same symptoms that you have. It may harm them.

You can ask your healthcare provider or pharmacist for information about ARCAPTA NEOHALER that is written for health professionals.

For more information about ARCAPTA NEOHALER or to report side effects, go to [www.arcapta.com](http://www.arcapta.com) or call 1-888-669-6682

### **What are the ingredients in ARCAPTA NEOHALER?**

**Active ingredient:** indacaterol

**Inactive ingredients:** lactose monohydrate (contains trace levels of milk protein)

Manufactured by:

Novartis Pharmaceuticals Corporation

East Hanover, New Jersey 07936

This Patient Information has been approved by the U.S. Food and Drug Administration.

Revised: July 2021

T2021-107

## **INSTRUCTIONS FOR USE**

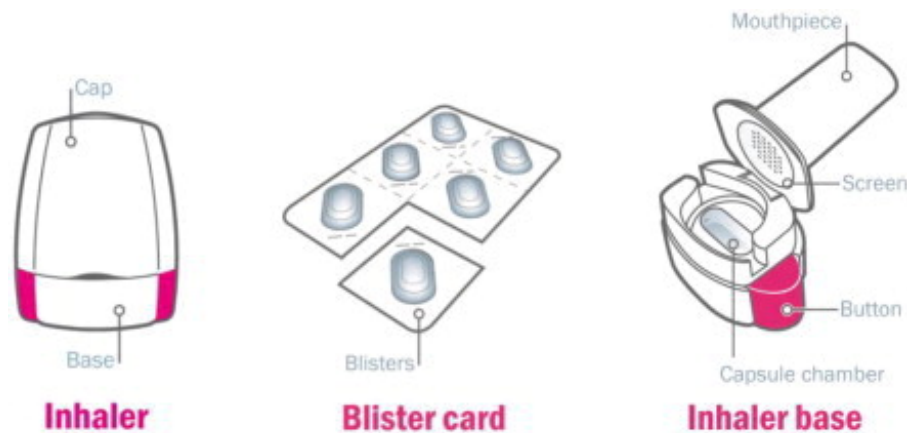
### **ARCAPTA® [ar-CAP-ta] NEOHALER®**

#### **(indacaterol) inhalation powder**

#### **Do not swallow ARCAPTA capsules.**

Follow the instructions below for using ARCAPTA NEOHALER. You will breathe-in (inhale) the medicine in the ARCAPTA capsules from the NEOHALER inhaler. If you have any questions, ask your healthcare provider or pharmacist.

### **ARCAPTA NEOHALER**



ARCAPTA NEOHALER consists of both the inhaler and the blister-packaged capsules. Each package contains ARCAPTA capsules and a NEOHALER inhaler.

- ARCAPTA capsules come in blister cards (see Figure above).
- NEOHALER inhaler consists of a cap and a base (see Figure above).

Your inhaler is made to give you the medicine contained in the capsules.

**Do not** use ARCAPTA capsules with any other capsule inhaler, and **do not** use NEOHALER inhaler to take any other capsule medicine.

## How to use your inhaler

### Figure A



**Step 1. Pull off cap. See Figure A**

### Figure B



**Step 2. Open inhaler: See Figure B**

Hold the base of the inhaler firmly and tilt the mouthpiece to open the inhaler.

### Figure C



**Step 3. Prepare capsule: See Figure C**

Separate one of the blisters from the blister card by tearing along the perforation.

Take one blister and peel away the protective backing to expose the foil.

### Figure D



**Step 4. Remove an ARCAPTA capsule: See Figure D**

**Capsules should always be stored in the blister and only removed immediately before use.**

With dry hands, remove one capsule from the blister by pushing the ARCAPTA capsule through the foil.

**Do not swallow ARCAPTA capsule.**

### Figure E

**Step 5. Insert capsule: See Figure E**

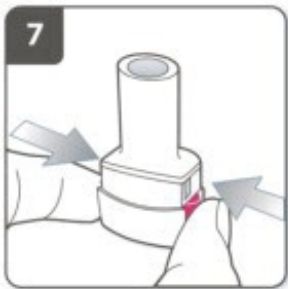
Place the capsule into the capsule chamber.



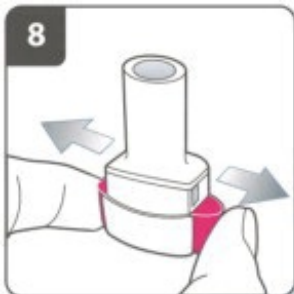
**Figure F**



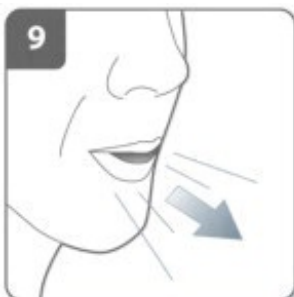
**Figure G**



**Figure H**



**Figure I**



**Figure J**

**Do not place a capsule directly into the mouthpiece.**

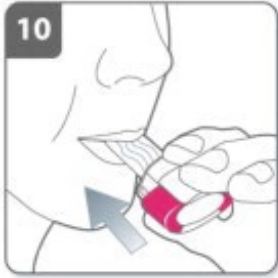
**Step 6. Close the inhaler: See Figure F**  
Close the inhaler fully. You should hear a **'click'** as it fully closes.

**Step 7. Pierce the capsule: See Figure G**  
Hold the inhaler upright.  
Press both buttons fully one time. You should hear a **'click'** as the capsule is being pierced.  
**Do not press the piercing buttons more than one time.**

**Step 8. Release the buttons fully. See Figure H**

**Step 9. Breathe out: See Figure I**  
Before placing the mouthpiece in your mouth, breathe out fully.  
**Never blow into the mouthpiece.**

**Step 10. Inhale the medicine: See Figure J**



**Figure K**



**Figure L**



**Figure M**



Before breathing in, place the mouthpiece in your mouth and close your lips around the mouthpiece. Hold the inhaler with the buttons to the left and right (not up and down). Breathe in rapidly and steadily, as deeply as you can. **Do not press the piercing buttons.**

**Note: See Figure K**

As you breathe in through the inhaler, the capsule spins around in the chamber and you should hear a whirring noise. If you do not hear a whirring noise, the capsule may be stuck in the capsule cavity. If this occurs, open the inhaler and carefully loosen the capsule by tapping the base of the device. Do not press the piercing buttons to loosen the capsule. **(Repeat steps 9 and 10 if needed.)**

**Step 11. Hold breath: See Figure L**

**Continue to hold your breath** as long as comfortably possible while removing the inhaler from your mouth. Then breathe out. Open the inhaler to see if any powder is left in the capsule. **If there is powder left in the capsule, close the inhaler and repeat steps 9 to 12.** Most people are able to empty the capsule in one or two inhalations.

Some people may cough soon after inhaling the medicine. If you do, don't worry, as long as the capsule is empty, you have received the full dose.

**Step 12. Remove capsule: See Figure M**

After you have finished taking your daily dose of the ARCAPTA NEOHALER, open the mouthpiece again, remove the empty capsule by tipping it out, and discard it. Close the inhaler and replace the cap. **Do not store the capsules in the NEOHALER device.**

**Additional Information**

Occasionally, very small pieces of the capsule can get past the screen and enter your mouth. If this happens, you may be able to feel these pieces on your tongue. It is not harmful if these pieces are swallowed or inhaled. **The chances of the capsule shattering will be increased if the capsule is pierced more than once (Step 7).** Therefore, it is recommended that you follow the storage directions, remove the capsule from the blister immediately before use and pierce each capsule only once.

## **How to clean your inhaler**

Cleaning the device is not necessary, however, if desired, a clean, dry lint-free cloth, or a clean, dry soft brush may be used to wipe the inhaler between uses.

### **Remember:**

- ARCAPTA capsules should be stored in the blister, and only removed immediately before use.
- Do not breathe into the NEOHALER inhaler.
- Do not place the ARCAPTA capsule directly into the mouthpiece of the NEOHALER inhaler.
- Do not store the ARCAPTA capsule in the NEOHALER inhaler chamber.
- Always release the push buttons prior to inhalation.
- Do not wash the NEOHALER inhaler. **Keep it dry.**
- Always keep the NEOHALER inhaler and ARCAPTA capsules in a dry place.
- Always use the new NEOHALER inhaler that comes with your refill.
- Do not use ARCAPTA capsules with inhalers from other medicines.
- Keep this and all drugs out of the reach of children.

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: July 2021

Manufactured by:

Novartis Pharmaceuticals Corporation

East Hanover, New Jersey 07936

T2021-108

## **PRINCIPAL DISPLAY PANEL**

CARTON LABEL - PRINCIPAL DISPLAY PANEL

NDC 63402-675-30

30 Capsules

Rx Only

Arcapta<sup>®</sup> Neohaler<sup>®</sup>

(indacaterol inhalation powder)

75 mcg per capsule

## **FOR ORAL INHALATION ONLY**

**Do not swallow the Arcapta capsules**

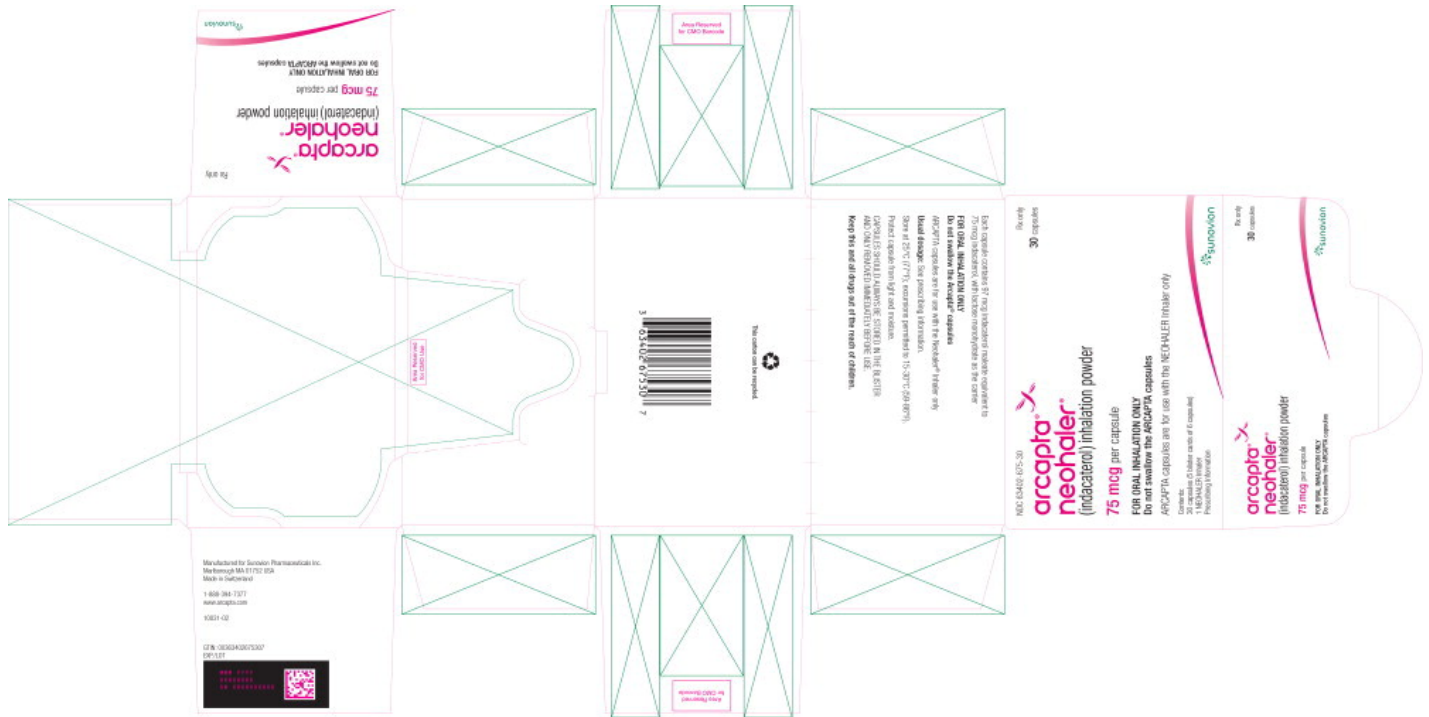
Contents:

30 Capsules (5 blister cards of 6 capsules)

1 NEOHALER Inhaler

Prescribing Information

GTIN: 00363402675307



## PRINCIPAL DISPLAY PANEL

BLISTER LABEL - PRINCIPAL DISPLAY PANEL

NDC 63402-675-01

5 blister cards of 6 capsules

Arcapta® Neohaler®

(indacaterol inhalation powder)

75 mcg per capsule

For use with NEOHALER only

Do not swallow capsule

Rx only

EXP/Lot

Manufactured for Sunovion



<b>ARCAPTA NEOHALER</b>			
indacaterol maleate capsule			
<b>Product Information</b>			
<b>Product Type</b>	HUMAN PRESCRIPTION DRUG	<b>Item Code (Source)</b>	NDC:63402-675
<b>Route of Administration</b>	ORAL, RESPIRATORY (INHALATION)		
<b>Active Ingredient/Active Moiety</b>			
<b>Ingredient Name</b>		<b>Basis of Strength</b>	<b>Strength</b>
INDACATEROL MALEATE (UNII: 2JEC1TX7R) (INDACATEROL - UNII:8OR09251MQ)		INDACATEROL	75 ug
<b>Inactive Ingredients</b>			
<b>Ingredient Name</b>			<b>Strength</b>
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)			
<b>Product Characteristics</b>			
<b>Color</b>	yellow (yellow)	<b>Score</b>	no score
<b>Shape</b>	CAPSULE (CAPSULE)	<b>Size</b>	16mm
<b>Flavor</b>		<b>Imprint Code</b>	IDL75;SPLSYMBOL
<b>Contains</b>			

**Packaging**

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:63402-675-30	5 in 1 CARTON	06/01/2017	01/31/2021
1	NDC:63402-675-01	6 in 1 BLISTER PACK; Type 1: Convenience Kit of Co-Package		
2	NDC:63402-675-06	1 in 1 CARTON	06/01/2017	01/31/2021
2	NDC:63402-675-02	6 in 1 BLISTER PACK; Type 1: Convenience Kit of Co-Package		

**Marketing Information**

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA022383	07/01/2011	01/31/2021

**Labeler** - Sunovion Pharmaceuticals Inc. (131661746)

Revised: 7/2021

Sunovion Pharmaceuticals Inc.