For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

Tiotropium Bromide and Formoterol Fumarate Rotacap

Duova

Rotacaps

For use with Rotahaler

Dosage Form: Capsule for inhalation

COMPOSITION

Each capsule contains

Tiotropium ..... 18 mcg
As Tiotropium bromide monohydrate
Formoterol fumarate.....12 mcg
Excipient.....q.s
Approved colours used in empty capsule

Description: White powder partially filled in hard gelatin capsules of size'3' with light green opaque cap and colourless transparent body.

PHARMACOLOGY

Pharmacodynamics

Tiotropium bromide: Tiotropium bromide has a quaternary ammonium structure and acts as an anticholinergic bronchodilator. Orally inhaled tiotropium bromide antagonizes the muscarinic M1, M2 and M3 receptors located in airway smooth muscle, reversing vagally mediated bronchoconstriction.Receptor binding assays and in vitro tests indicate that tiotropium bromide is kinetically selective for M1 and M3 receptors over the M2 receptor, unlike ipratropium bromide, which is nonselective. Animal and in vitro studies showed that tiotropium bromide was more potent (~ 20-fold) than ipratropium bromide in displacing [3H] N-methylscopolamine (NMS) from muscarinic receptors, and had a more sustained protective effect (> 70% inhibition) against NMS binding. Tiotropium bromide was a more potent inhibitor of bronchial contraction than atropine (~ 23-fold), and had a slower onset and markedly longer duration of action than atropine or an equipotent dose of ipratropium bromide. Aerosol particle penetration is improved with tiotropium, without delaying mucus clearance from the lungs. Tiotropium 4.5-36 mcg once daily for 4 weeks increased mean trough and average FEV1 and FVC and mean PEFR values from baseline compared with placebo, with no evidence of tachyphylaxis. The optimal once-daily tiotropium dosage is 18 mcg. The long duration is probably due to the very slow dissociation from the M3 receptor, exhibiting a significantly longer dissociation half-life than ipratropium.

Steady-state trough FEV1 values are achieved within 48 hours of commencing tiotropium. The drug improved static and dynamic lung hyperinflation and exercise tolerance compared with placebo in randomized, double-blind studies.

Special Populations

Elderly patients: As expected for drugs predominantly excreted renally advanced age was associated with a decrease of tiotropium renal clearance which may be explained by decreased renal function.

Hepatic impairment: The effects of hepatic impairment on the pharmacokinetics of tiotropium has not been studied. However hepatic insufficiency is not expected to have any influence on tiotropium pharmacokinetics.

Renal impairment: In COPD patients with moderate to severe renal impairment (creatinine clearance < 50 ml/min) the intravenous administration of tiotropium resulted in doubling of the plasma concentrations (82% increase in AUC $_{0-4}$) which was confirmed by plasma concentrations after dry powder inhalation.

Formoterol Fumarate: Formoterol is a potent selective beta$_2$-adrenergic stimulant. It exerts bronchodilator effects in patients with reversible airways obstruction. The effect sets in rapidly (within 1-3 minutes) and is still significant 12 hours after inhalation. Bronchodilation is significant within minutes of inhalation, maximal within 2 hours and at therapeutic doses is equivalent to that produced by standard doses of traditional (beta$_2$ agonists). The therapeutic efficacy of inhaled formoterol has been equal to or greater than that of salbutamol (albuterol), fenoterol and terbutaline in both short and long term clinical trials. Formoterol has been studied in the treatment of COPD, and has been shown to improve symptoms and pulmonary function and quality of life.

The combination of tiotropium and formoterol produces additive effects since they target different receptors in the airways.

Pharmacokinetics

Tiotropium bromide Mean maximal plasma concentrations (Cmax) were observed within 5 minutes of inhalation of a single dose of tiotropium 18mcg in patients with COPD. Plasma drug levels declined to minimum concentrations (Cmin) within 1 hour of treatment in healthy volunteers. Mean steady-state Cmax concentrations (16 ng/L) were achieved after 2-3 weeks of once-daily inhaled tiotropium 18mcg in elderly patients with COPD; tiotropium does not appear to accumulate once steady state has been achieved. The estimated absolute bioavailability of tiotropium at steady state in healthy volunteers was approximately 20-25%, and approximately 72% of the drug is bound to plasma proteins. Excretion of tiotropium is predominantly renal (through active secretion by the kidneys), although in vitro studies suggest that cytochrome P450 (CYP) oxidation (possibly involving CYP2D6 and CYP3A4 enzymes) may have a minor role. In patients with COPD, renal excretion of the unchanged drug at 24 hours (Ae24) was approximately 7%. The mean plasma elimination half-life after single or multiple doses in healthy volunteers and elderly patients with COPD was approximately 5-6 days. The renal clearance and urinary excretion of tiotropium decrease with increasing age; however, these changes are not considered to be clinically significant. Tiotropium does not interact with drugs such as cimetidine or ranitidine, which are also eliminated by renal secretion.

Formoterol fumarate: Following inhalation of formoterol 24 mcg, 24% of the dose is excreted in the urine in 12 hours. After oral (systemic) formoterol 40 mcg, urinary excretion is 9.6% in 24 hours. Mean peak concentration (Cmax) was 70.1 ng/L and half-life was 3.4 hours. Cmax values of about 160 ng/L have been previously reported after repeated oral doses of 40 to 80 mcg.

The pharmacokinetics of a single 120 mcg dose of inhaled formoterol were studied in healthy volunteers. Inhalation of a single dose of formoterol 120 mcg appeared to result in a biphasic pattern of kinetics in serum, with an initial Cmax of 52 ng/L occurring at 0.25 hours. Following a lag period, a second Cmax of 40 ng/L occurred at 1.58 hours.

TOXICOLOGY

Toxicity

Tiotropium: No mortality was observed at inhalation tiotropium doses up to 32.4 mg/kg in mice. 257.7 mg/kg in rats and 0.6 mg/kg in dogs. These doses correspond to 7,300. 120.000 and 850 times the recommended human daily dose on a mg/m2 basis respectively.

Formoterol: The minimum acute lethal inhalation dose of formoterol fumarate in rats is 156 mg/kg (approximately 53.000 and 25.000 times the maximum recommended daily inhalation dose in adults and children respectively on a mg/m2 basis). The median lethal oral doses in Chinese hamsters, rats and mice provide even higher multiples of the maximum recommended daily inhalation dose in humans.

Carcinogenesis

Tiotropium: No evidence of tumorigenicity was observed in a 104-week inhalation study in rats at tiotropium doses up to 0.059 mg/kg/day, in an 83-week inhalation study in female mice at doses up to 0.145 mg/kg/day, and in a 101-week inhalation study in male mice at doses up to 0.002 mg/kg/day. These doses correspond to 23.35 and 0.5 times the recommend human daily dose on mg/m^2 basis respectively.

Formoterol: The carcinogenic potential of formoterol fumarate has been evaluated in 2-year drinking water and dietary studies in both rats and mice. In rats, the incidence of ovarian leiomyomas was increased at doses of 15 mg/kg and above in the drinking water study and at 20 mg/kg in the dietary study, but not at dietary doses up to 5 mg/kg (AUC exposure approximately 450 times human exposure at the maximum recommended daily inhalation dose).

Mutagenesis

Tiotropium: Tiotropium bromide demonstrated no evidence of mutagenicity or clastogenicity in the following assays: the bacterial gene mutation assay, the V79 Chinese hamster cell mutagenesis assay, the chromosomal aberration assays in human lymphocytes in vitro and mouse micronucleus formation in vivo, and the unscheduled DNA synthesis in primary rat hepatocytes in vitro assay.

Formoterol: Formoterol fumarate was not mutagenic or clastogenic in the following tests: mutagenicity tests in bacterial and mammalian cells, chromosomal analyses in mammalian cells, unscheduled DNA synthesis repair tests in rat hepatocytes and human fibroblasts, transformation assay in mammalian fibroblasts and micronucleus tests in mice and rats.

Impairment of Fertility

Tiotropium:In rats, decreases in the number of corpora lutea and the percentage of implants were noted at inhalation tiotropium doses of 0.078 mg/kg/day or greater (approximately 35 times the Recommended Human Daily Dose on a mg/m^2 basis). No such effects were observed at 0.009 mg/kg/day (approximately 4 times than the recommended human daily dose on a mg/m^2 basis. The fertility index, however, was not affected at inhalation doses up to 1689 mg/kg/day (approximately 760 times the recommended human daily dose on a mg/m2 basis.

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

Teratogenicity

Tiotropium: No evidence of structural alterations was observed in rats and rabbits at inhalation tiotropium doses of up to 1.471 and 0.007 mg/kg/day, respectively. These doses correspond to approximately 660 and 5 times the recommended human daily dose on a mg/m^2 basis. However, in rats, fetal resorption, litter loss, decreases in the number of live pups at birth and the mean pup weights and a delay in pup sexual maturation were observed at inhalation tiotropium doses of 0.078 mg/kg (approximately 35 times the recommended human daily dose on a mg/m^2 basis). In rabbits, an increase in post-implantation loss was observed at an inhalation dose of 0.4 mg/kg/day (approximately 360 times the recommended human daily dose on a mg/m^2 basis). Such effects were not observed at inhalation doses of 0.009 and up to 0.088 mg/kg/day in rats and rabbits respectively. These doses correspond to approximately 4 and 80 times the Recommended Human Daily dose on a mg/m^2 basis respectively.

Formoterol: Formoterol fumarate has been shown to cause stillbirth and neonatal mortality at orsl doses of 6 mg/kg (approximately 2000 times the maximum recommended daily inhalation dose in humans on a mg/m^2 basis) and above in rats receiving the drug during the late stage of pregnancy. These effects, however, were not produced at a dose of 0.2 mg/kg (approximately 70 times the maximum recommended daily inhalation dose in humans on a mg/m^2 basis.

INDICATIONS

DUOVA is indicated in the maintenance treatment of chronic obstructive pulmonary disease (COPD).

DOSAGE AND ADMINISTRATION

The recommended dosage is the inhalation of the contents of one rotacap once daily. DUOVA Rotacaps should only be inhaled with the Cipla Rotahaler device. DUOVA Rotacaps must not be swallowed.

CONTRAINDICATIONS

DUOVA Rotacaps are contraindicated in patients with a hypersensitivity to atropine or its derivatives (e.g. ipratropium and oxitropium), formoterol, lactose monohydrate or any other component of the product.

WARNINGS AND PRECAUTIONS

Since DUOVA contains a combination of tiotropium and formoterol the warning and precautions for both drugs should be observed. DUOVA Rotacaps, as a once daily maintenance bronchodilator should not be used for the initial treatment of acute episodes of bronchospasm i.e. rescue therapy. DUOVA Rotacaps should be used with caution in patients with narrow angle glaucoma, prostatic hyperplasia or bladder-neck obstruction.

Tiotropium bromide being a predominantly renally excreted drug, patients with moderate to severe renal impairment (creatinine clearance of < 50 ml/min) treated with DUOVA Rotacaps should be monitored closely. Patients should be cautioned to avoid getting the contents of DUOVA Rotacaps into their eyes. This might result in precipitation or worsening of narrow-angle glaucoma, eye pain or discomfort, temporary blurring of vision, visual halos or coloured images in association with red eyes from conjuctival and corneal congestion. Patients should stop using DUOVA Rotacaps and consult a physician immediately.

DUOVA Rotacaps should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias or hypertension. Patients should be cautioned about potential adverse cardiovascular effects such as palpitations. Potentially serious hypokalaemia may result from beta-agonist therapy. This may be augmented by concomitant treatment with xanthine derivatives, steroids, diuretics, and by hypoxia. The serum potassium levels should therefore be monitored in such situations. As with other inhalation therapy, the potential for paradoxical bronchospasm should be considered. If it occurs, the preparation should be discontinued immediately.

Drug Interactions

Concomitant administration of other oral beta-stimulan
substances with a similar type of action must be avoi
potentiated cardiovascular effects. Concomitant treati
derivatives, steroids, or diuretics may potentiate a pos
beta-agonists. Hypokalaemia may increase susceptil
in patients treated with digitalis. Concomitant treatme
disopyramide, procainamide, phenothiazines, antihist
monoamine oxidase inhibitors and tricyclic antidepres
interval and increase the risk of ventricular arrhythmi
L-thyroxine, oxytocin and alcohol can impair cardiac t
ympathomimetics. Beta-adrenergic blockers (includin
inhibit the effect of formoterol.There is an elevated ris
receiving concomitant anaesthesia with halogenated
The co-administration of DUOVA with other anticholir
not been studied and is therefore not recommended.

Pregnancy

Use of DUOVA during pregnancy should be consider
the mother is greater than the risk to the foetus.

Lactation

Since it is not known whether the active substance pa
DUOVA is not recommended for use during lactation.

Paediatric Use

Safety and effectiveness of tiotropium bromide inhala
has not been established and therefore DUOVA shou
under 18 years of age.

SIDE EFFECTS

As the combination contains tiotropium + formoterol,
effects associated with each of the compounds may
Tiotropium: Possible adverse events attributable to sys
include dry mouth, dry throat, increased heart-rate, b
urinary difficulty, urinary retention and constipation.
The most common anticholinergic adverse reaction r
was dry mouth, which was mild in the majority of case
an onset between three and five weeks, which resolv
to receive tiotropium bromide. Discontinuation rates c
of the treated patients.
Formoterol: Tremor, palpitations and headache have b
tend to be transient and reduced with regular therapy.
cramps and hypersensitivity reactions including rash, c
occur in some patients.

OVERDOSAGE

There are no data on overdosage with Tiotropium + F
tiotropium bromide may lead to anticholinergic signs
effects). However, there were no systemic anticholin
following a single inhaled dose of up to 340 mcg tiotr
volunteers. Additionally, no relevant adverse effects,
observed following seven-day dosing of up to 170 m
healthy volunteers. Acute intoxication by inadvertent
bromide is unlikely due to low oral bioavailability.
The signs and symptoms of formoterol overdose are
tachycardia. The preferred antidotes are cardioselec
agents, which should be used with caution in patient
bronchospasm.

Storage Condition : Store below 30°C. Protect from h

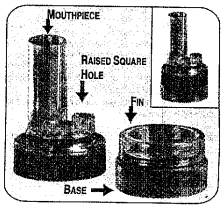
Presentation

DUOVA Rotacaps.....Container of 15 capsule

CIPLA LTD.
Mumbai Central Mumbai 400 008 INDIA

Cipla

Patient Information Leaflet



THE ROTAHALER

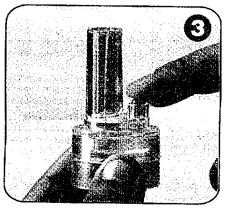
The transparent Rotahaler is specially designed for easy and convenient use to help you obtain full benefit of the medicine.

PREPARING THE ROTAHALER FOR USE

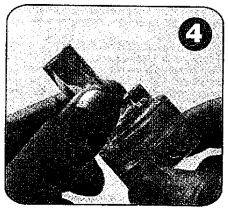
Hold the Rotahaler vertically as shown.

Note: It is important to position the two halves of the Rotahaler such that the fin is not directly below the raised square hole.

Take a Rotacap capsule from its container. Insert the Rotacap, transparent end first, into the raised square hole of the Rotahaler.



Press the Rotacap firmly such that the top end of the Rotacap is in level with the top of the hole.



Holding the mouthpiece firmly with one hand, rotate the base. The fin separates the two halves of the Rotacap as can be seen through the transparent body of the Rotahaler. The Rotahaler is now ready for use.

USING THE ROTAHALER

Breathe out fully.

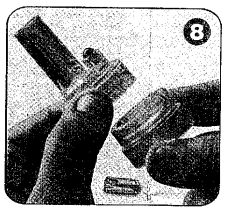
Grip the mouthpiece between your teeth and seal your lips around it. Tilt your head slightly backwards. Breathe in through your mouth as deeply as you can.

Note: If you are doing this correctly you will hear the Rotacap shell rattling inside the Rotahaler.

Hold your breath for 10 seconds or for as long as it is comfortable. Breathe out slowly

At times, 1 or 2 additional inhalations may be required to ensure that the dose is taken. For this purpose, repeat steps 5 to 7.

AFTER USING THE ROTAHALER



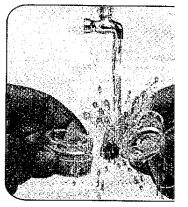
After use, separate the two halves of the Rotahaler and discard the empty Rotacap shell. Reassemble the Rotahaler for subsequent use.

FOR SUBSEQUENT USE: Insert a fresh Rotacap as shown in step 2. The shell lodged in the square hole (from previous use) will be pushed out when the fresh Rotacap is inserted. Proceed with steps 3 through 8.

CARE OF THE ROTAHA

Wash the Rotahaler at l a week.

- Separate the two halves Rotahaler.
- Remove the empty Rota from the raised square h



- Rinse the two halves in run tap water.
- Shake well to remove exces water and leave to dry. Avoi the use of heat.
- Reassemble the two halves for subsequent use.

CAUTION: Do not push any cle cloth or instrument into the mouthpiece as this may dama the Rotahaler.

NOTE

Always store the Rotahaler in its box to keep it clean. It is recomn that a fresh Rotahaler is used ev six months. Use only as directed your doctor. If the recommendec does not provide relief of sympto symptoms become worse, consu your doctor. Keep the container containing the Rotacaps tightly c Insert the Rotacap in the Rotaha just prior to use, as Rotacaps exp to moisture may not break open At times, a fine layer of powder n observed in the Rotacap shell aft use. This does not affect the effic of the medicine.