INTERACTIONS:
Although no formal drug interaction studies have been performed, Tiotropium bromide has been used concomitantly with other drugs, commonly used in the treatment of COPD, including sympathomimetic bronchodilators, methylxanthines, oral and inhaled steroids without clinical evidence of drug interactions.

Common concomitant medications (LABA, ICS and their combinations) used by patients with COPD were not found to alter the exposure to Tiotropium.

Limited information about co-administration of other anticholinergic drugs with Tiotropium bromide is available from two clinical trials: Acute single dose administration of ipratropium bromide with chronically administered Tiotropium bromide in COPD patients (n=64) and healthy volunteers (n=35) was not associated with an increase in adverse events, changes in vital signs or electrocardiographic findings. However, chronic co-administration of other anticholinergic drugs with Tiotropium bromide has not been studied and is, therefore, not recommended.

ADVERSE EFFECTS:
Many of the listed undesirable effects can be assigned to the anticholinergic properties of Tiotropium bromide.

Adverse drug reactions were identified from data obtained in clinical trials and spontaneous reporting during post approval use of the drug. The clinical trial database includes 9,647 tiotropium patients from 28 placebo-controlled clinical trials with treatment periods ranging between four weeks and four years, contributing 12,469 person years of exposure to Tiotropium.

Metabolism and nutrition disorders:
- Dehydration

Nervous system disorders:
- Dizziness
- Insomnia

Eye disorders:
- Vision blurred
- Glaucoma
- Intraocular pressure increased

Cardiac disorders:
- Atrial fibrillation
- Supraventricular tachycardia
- Tachycardia
- Palpitations

Respiratory, thoracic and mediastinal disorders
- Cough
- Dysphonia
- Pharyngitis
- Bronchospasm
- Epistaxis
- Laryngitis
- Sinusitis

Gastrointestinal disorders
- Dry mouth, usually mild
- Constipation
- Gastroesophageal reflux disease
- Oropharyngeal obstruction incl. ileus paralytic
- Dysphagia
- Gingivitis
- Glossitis
- Stomatitis

Skin and subcutaneous tissue disorder, Immune system disorders:
- Rash
- Angioedema
- Hypersensitivity (including immediate reactions)
- Pruritus
- Urticaria
- Dry skin
- Skin infection and skin ulcer

Musculoskeletal and connective tissue disorders:
- Joint swelling

Renal and urinary disorders:
- Urinary retention (usually in men with predisposing factors)
- Dysuria
- Urinary tract infection

OVERDOSE AND TREATMENT:
High doses of Tiotropium bromide may lead to anticholinergic signs and symptoms.

However, there were no systemic anticholinergic adverse effects following a single inhaled dose of up to 282 micrograms Tiotropium in healthy volunteers.

Bilateral conjunctivitis in addition to dry mouth was seen in healthy volunteers following repeated once daily inhalation of 141 micrograms in healthy volunteers, which resolved while still under treatment. In a multiple dose study in COPD patients with a maximum daily dose of 36 micrograms Tiotropium over four weeks dry mouth was the only observed adverse even attributable to Tiotropium.

Acute intoxication by oral ingestion of Tiotropium capsules is unlikely due to low oral bioavailability.

STORAGE CONDITION:
Store at temperatures not exceeding 30°C.

AVAILABILITY:
1 carton containing 1 box of 5 alu-alu blister pack x 8's + 1 inhaler device in a box.

Manufactured for:
DR. ZEN'S RESEARCH, INC.
71 Scout Fernandez, Laging Handa, Quezon City

Manufactured by:
LLOYD LABORATORIES, INC.
No. 10 Lloyd Avenue, First Bulacan Industrial City,
Malolos, Bulacan

CAUTION:
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

ADR REPORTING STATEMENT:
"For suspected adverse drug reaction, report to FDA: www.fda.gov.ph." Seek medical attention immediately at the first sign of any adverse drug reaction.

Registration Number: DR-XY46937

Date of First Authorization: 17 September 2020

Date of Revision of Package Insert: October 2023

TIOTROPIUM

18 mcg
Pre-metered Dose Dry Powder for Inhalation
ANTICHOLINERGIC

FORMULATION:
Each capsule contains:
Tiotropium (as bromide) ..... 18 mcg
(equivalent to 10 mcg delivered dose)

PRODUCT DESCRIPTION:
Tiotropium bromide 18 mcg Pre-metered Dose Dry Powder for Inhalation is a white to off-white powder encapsulated in hard gelatin capsule of size 3 with transparent body and cap.

PHARMACOLOGIC PROPERTIES:
Pharmacotherapeutic group: Other drugs for obstructive airways diseases, inhalants, anticholinergics;
ATC code: R03BB04

Tiotropium is a long-acting, specific antimuscarinic agent, in clinical medicine often called an anticholinergic. It has a similar affinity of the subtypes of muscarinic receptors M_1 to M_5. In the airways, inhibition of M_3-receptors at the smooth muscle results in relaxation. The competitive and reversible nature of antagonism was shown with human and animal origin receptors and isolated organ preparations. In non-clinical *in vitro* as well as *in vivo* studies bronchoprotective effects were dose-dependent and lasted longer than 24 hours. The long duration of effect is likely to be due to its very slow dissociation from M_3-receptors, exhibiting a significantly longer dissociation half-life than that seen with ipratropium. As a N-quaternary anticholinergic Tiotropium is topically (broncho-) selective when administered by inhalation, demonstrating an acceptable therapeutic range before giving rise to systemic anticholinergic effects. Dissociation from M_2-receptors is faster than from M_3 which in functional *in vitro* studies, elicited (kinetically controlled) receptor subtype selectivity of M_3 and M_2.

The high potency and slow receptor dissociation found its clinical correlate in significant and long-acting bronchodilation in patients with COPD.

The bronchodilation following inhalation of Tiotropium is primarily a local effect (on the airways) not a systemic one.

Cardiac electrophysiology
In a dedicated QT study involving 53 healthy volunteers, Tiotropium bromide 18 mcg and 54 mcg (i.e. three times the therapeutic dose) over 12 days did not prolong QT intervals of the ECG.

Clinical efficacy
The clinical development program included four one-year and two six-month randomized, double-blind studies in 2663 patients with COPD (1308 receiving Tiotropium bromide). The one-year program consisted of two placebo-controlled and two ipratropium-controlled trials. The six-month trials were both salmeterol- and placebo-controlled. These studies included evaluation of lung function, dyspnea, exacerbations of COPD and patients assessments of their health-related quality of life.

Lung Function
Tiotropium bromide administered once daily, provided significant improvement in lung function (forced expiratory volume in one second, FEV_1 and forced vital capacity, FVC) within 30 minutes following the first dose and was maintained for 24 hours. Pharmacodynamic steady state was reached within one week with the majority of bronchodilation observed by the third day. Tiotropium bromide significantly improved morning and evening peak expiratory flow rate (PEFR) as measured by patient's daily recordings.

The improvement in lung function with Tiotropium bromide was demonstrated throughout the period of administration in the six long-term trials. These improvements were maintained with no evidence of tolerance.

A randomized, placebo-controlled clinical study in 105 patients with COPD demonstrated that bronchodilation was maintained throughout the 24 hour dosing interval in comparison to placebo regardless of whether Tiotropium bromide was administered in the morning or in the evening.

Long-term clinical trials (6 months and 1 year)

Dyspnea, Exercise tolerance
Tiotropium bromide significantly improved dyspnea (as evaluated using the Transition Dyspnea Index). This improvement was maintained throughout the treatment period.

The impact of improvement in dyspnea on functional activities was investigated in two randomized double blind placebo controlled trials in COPD patients. In these trials Tiotropium bromide significantly improved symptom limited exercise tolerance by 19.7% and 28.3% compared with placebo.

Health-related Quality of Life
Tiotropium bromide significantly improved health-related quality of life as demonstrated by the disease-specific St. George's Respiratory Questionnaire. This improvement was maintained throughout the treatment period.

COPD Exacerbations
Tiotropium bromide significantly reduced the number of COPD exacerbations and delayed the time to first exacerbation in comparison to placebo.

Additionally, in the one year placebo controlled trials Tiotropium bromide significantly reduced the number of hospitalizations associated with COPD exacerbations and delayed the time to first hospitalization.

A one-year randomized, double-blind, double-dummy, parallel-group trial compared the effect of treatment with 18 mcg of Tiotropium bromide once daily with that 50 mcg of salmeterol HFA pMDI twice daily on the incidence of moderate and severe exacerbations in 7,376 patients with COPD and a history of exacerbation in the preceding year.

Table 1: Summary of Exacerbation endpoints

Endpoint	Tiotropium bromide 18 mcg N= 3,707	Salmeterol 50 mcg (HFA pMDI) N=3,669	Ratio (95% CI)	p-value
Time [days] to first exacerbation[†]	187	145	0.83 (0.77 – 0.90)	<0.001
Time to first severe (hospitalized) exacerbation[§]	-	-	0.72 (0.61 – 0.85)	<0.001
Patients with ≥1 exacerbation, *n* (%)*	1,277 (34.4)	1,414 (38.5)	0.90 (0.85 – 0.95)	<0.001
Patients with ≥1 severe (hospitalized) exacerbation, *n* (%)*	262 (7.1)	336 (9.2)	0.77 (0.66 – 0.89)	<0.001
Mean exacerbation incidence rate per patient year[#]	0.64	0.72	0.89 (0.83 – 0.96)	=0.002

Mean severe (hospitalized) exacerbation incidence rate per patient year[#]	0.09	0.13	0.73 (0.66 – 0.82)	<0.001

[*]Time [days] refers to 1st quartile of patients. Time to event analysis was done using Cox's proportional hazards regression model with (pooled) center and treatment as covariate; ratio refers to hazard ratio.

§Time to event analysis was done using Cox's proportional hazards regression model with (pooled) center and treatment as covariate; ratio refers to hazard ratio. Time [days] for the 1st quartile of patients cannot be calculated, because proportion of patients with severe exacerbation is too low.

[*]Number of patients with event were analyzed using Cochran-Mantel-Haenszel test stratified by pooled center; ratio refers to risk ratio.

[#]Number of event analysis was done using Poisson regression correction for overdispersion and adjusting for treatment exposure; ratio refers to rate ratio.

Compared with salmeterol, Tiotropium bromide increased the time to the first exacerbation (187 days vs. 145 days), with a 17% reduction in risk (hazard ration, 0.83; 95% confidence interval [CI], 0.77 to 0.90; P<0.001). Tiotropium bromide also increased the time to the first severe (hospitalized) exacerbation (hazard ratio, 0.72; 95% CI, 0.61 to 0.85; P<0.001), reduce the annual number of moderate or severe (hospitalized) exacerbations (0.64 vs. 0.72; rate ration 0.89; 95% CI, 0.83 to 0.96; P=0.002), and reduced the annual number of severe (hospitalized) exacerbations (0.09 vs. 0.13; rate ratio, 0.73; 95% CI, 0.66 to 0.82; P<0.001).

Long term clinical trials (>1 up to 4 years)

In a 4-year trial of 5,993 patients Tiotropium bromide maintained improvements in FEV_1 throughout 4 years but did not alter the annualized rate of decline of FEV_1.

During treatment, there was a 16% reduction in the risk of death. The incidence rate of death was 4.79 per 100 patient years in the placebo group vs. 4.10 per 100 patient years in the Tiotropium group (hazard ration (Tiotropium/placebo) = 0.84), 95% CI=0.73, 0.97). Treatment with Tiotropium reduced the risk of respiratory failure by 19% (2.09 vs. 1.68 cases per 100 patient years, relative risk (Tiotropium/placebo) = 0.81, 95% CI=0.65, 1.00).

Long-term Tiotropium active-controlled study

A long term, large scale, randomized, double-blind, active-controlled study with a treatment period up to 3 years has been performed to compare the efficacy and safety of Tiotropium bromide (5,711 patients receiving Tiotropium bromide) 2.5 microgram (5 microgram medicinal dose); 5,694 patients receiving the dose. The primary endpoints were time to first COPD exacerbation, time to all-cause mortality and in a sub-study (906 patients) trough FEV_1 (pre-dose).

The time to first COPD exacerbation was similar during the study with Tiotropium bromide and the Handihaler (hazard ratio (Tiotropium bromide/Handihaler)) 0.98 with a 95% CI of 0.93 to 1.03. The median number of days to the first COPD exacerbation was 756 days for Tiotropium bromide and 719 days for the device.

The bronchodilator effect of Tiotropium bromide was sustained over 120 weeks, and was similar to the device. The mean difference in trough FEV_1 for Tiotropium bromide versus the handihaler was 0.0.10 L (95% CI -0.038 to 0.018 mL).

All-cause mortality was similar during the study with Tiotropium bromide and Handihaler ratio (Tiotropium bromide/Handihaler) 0.96 with a 95% CI of 0.84 to 1.09.

PHARMACOKINETICS:

Tiotropium is a non-chiral quaternary ammonium compound and is sparingly soluble in water. Tiotropium is administered by dry powder inhalation. Generally with the inhaled route of administration, the majority of the delivered dose is deposited in the gastrointestinal tract, and to a lesser extent in the intended organ of the lung. Many of the pharmacokinetic data described below were obtained with higher doses as recommended for therapy.

Absorption: following dry powder inhalation by young healthy volunteers, the absolute bioavailability of 19.5% suggests that the fraction reaching the lung is highly bioavailable.

Oral solutions of Tiotropium have an absolute bioavailability of 2-3%. Food is not expected to influence the absorption of Tiotropium for the same reason.

Maximum Tiotropium plasma concentrations were observed 5-7 minutes after inhalation. At steady state, peak Tiotropium plasma concentrations in COPD patients were 12.9 pg/mL and decreased rapidly in a multi-compartmental manner. Steady state trough plasma concentrations were 1.71 pg/mL.

Distribution: Tiotropium has a plasma protein binding of 72% and shows a volume of distribution of 32 L/kg. Local concentrations in the lung are not known, but the mode of administration suggests substantially higher concentrations in the lung. Studies in rats have shown that Tiotropium does not penetrate the blood-brain barrier to any relevant extent.

Biotransformation: The extent of biotransformation is small. This is evident from a urinary excretion of 75% of unchanged substance after an intravenous dose to young healthy volunteers. Tiotropium, an ester, is nonenzymatically cleaved to the alcohol N-methylscopine and dithienylglycolic acid, both not binding to muscarinic receptors.

In vitro experiments with human liver microsomes and human hepatocytes suggest that some further drug (<20% of dose after intravenous administration) is metabolized by cytochrome P450 dependent oxidation and subsequent glutathione conjugation to a variety of Phase II-metabolites. This enzymatic pathway can be inhibited by the CYP450 2D6 (and 3A4) inhibitors, quinidine, ketoconazole and gestodene. Thus CYP450 2D6 and 3A4 are involved in the metabolic pathway that is responsible for the elimination of a smaller part of the dose. Tiotropium even in supra-therapeutic concentrations does not inhibit cytochrome P450 1A1, 1A2, 2B6, 2C9, 2D6, 2E1, or 3A in human liver microsomes.

Elimination: The effective half-life of Tiotropium ranges between 27-45 h in healthy volunteers and COPD patients. Total clearance was 880 mL/min after an intravenous dose young healthy volunteers. Intravenously administered Tiotropium is mainly excreted unchanged in urine (74%). After dry powder inhalation to COPD patients to steady state, urinary excretion is 7% (1.3 µg) of the unchanged dose over 24 hours, the remainder being mainly non-absorbed drug in gut that is eliminated via the feces. The renal clearance of Tiotropium exceeds the creatinine clearance, indicating secretion into the urine. After chronic once daily inhalation by COPD patients, pharmacokinetic steady state was reached by day 7 with no accumulation thereafter.

Linearity/nonlinearity: Tiotropium demonstrates linear pharmacokinetics in the therapeutic range independent of the formulation.

Special Populations:

Elderly Patients: As expected for all predominantly renally excreted drugs, advancing age was associated with a decrease of Tiotropium renal clearance (365 mL/min in COPD patients < 65 years to 271 mL/min in COPD patients > 65 years). This did not result in a corresponding increase in $AUC_{0\text{-}6,ss}$ or $C_{max,ss}$ values.

Renally Impaired Patients: Following once daily inhaled administrations of Tiotropium to steady-state in COPD patients, with mild renal impairment (CL_{CR} 50-80 mL/min) resulted in slightly higher $AUC_{0\text{-}6,ss}$ (between 1.8-30% higher) and similar $C_{max,ss}$ values compared to patients with normal renal function (CL_{CR} > 80 mL/min).

In COPD patients with moderate to severe renal impairment (CL_{CR} <50 mL/min) the intravenous administration of Tiotropium resulted in doubling of the plasma concentrations (82% increase in $AUC_{0\text{-}4h}$) and 52% higher C_{max} compared to COPD patients with normal renal function, which was confirmed by plasma concentrations after dry powder inhalation.

Hepatically Impaired Patients: Liver insufficiency is not expected to have any relevant influence on Tiotropium pharmacokinetics. Tiotropium is predominantly cleared by renal elimination (74% in young healthy volunteers) and by simple non-enzymatic ester cleavage to products that do not bind to muscarinic receptors.

TOXICOLOGY:

The **acute inhalation and oral toxicity** in mice, rats, and dogs was low; therefore, toxic effects from acute human drug overdosage are unlikely. The single dose safety pharmacology studies showed the expected effects of an anticholinergic drug including mydriasis, increased heart rate and prolonged gastrointestinal transit time.

The side effects of the **repeated dose studies** in rats, mice and dogs were related to anticholinergic properties of Tiotropium including mydriasis, increased heart rate, constipation, decreased body weight gain, reduce salivary and lacrimal gland secretion. Other relevant changes noted were: mild irritancy of the upper respiratory tract in rats envinced by rhinitis and epithelial changes of the nasal cavity and larynx, and prostatitis along with proteinaceous deposits and lithiasis in the bladder of male rats, increased lung weights in rats and decreased heart weights in dogs.

In the **reproduction studies** in rabbits and rats harmful effects with respect to pregnancy, embryo/fetal development, parturition or postnatal development could only be demonstrated at maternally toxic dose levels. In a general reproduction and fertility study in rats, there was no indication of any adverse effect on fertility or mating performance of either treated parents of their offspring at any dosage.

In aeries of *in vivo* and *in vitro* **mutagenicity assays**, Tiotropium bromide monohydrate did not cause gene mutations in prokaryotes and in eukaryotes, chromosomal damage *in vitro* and *in vivo* conditions or primary DNA damage

INDICATIONS:

Tiotropium bromide is indicated for the maintenance treatment of patients with COPD (including chronic bronchitis and emphysema), the maintenance treatment of associated dyspnea and for prevention of exacerbations.

DOSAGE AND ADMINISTRATION:

The recommended dosage of Tiotropium bromide is inhalation of the contents of one capsule once daily with the inhalation device at the same time of day.

Tiotropium bromide capsules must not be swallowed.

Special population:

Elderly patients can use Tiotropium bromide at the recommended dose.

Renally impaired patients can use Tiotropium bromide at the recommended dose.

However, as with all predominantly renally excreted drugs, Tiotropium bromide use should be monitored closely in patients with moderate to severe renal impairment.

Hepatically impaired patients can use Tiotropium bromide at the recommended dose.

Pediatric population:

There is no experience with Tiotropium bromide in infants and children and therefore should not be used in this age group.

CONTRAINDICATIONS:

Tiotropium bromide inhalation powder is contraindicated in patients with a history of hypersensitivity to atropine or its derivatives, e.g ipratropium or oxitropium or to any component of this product.

SPECIAL WARNINGS AND PRECAUTIONS:

Tiotropium bromide, as a once daily maintenance bronchodilator, should not be used for the initial treatment of acute episodes of bronchospasm, i.e. rescue therapy.

Immediate hypersensitivity reactions may occur after administration of Tiotropium bromide inhalation powder.

As with other anticholinergic drugs, Tiotropium bromide should be used with caution in patients with narrow-angle glaucoma, prostatic hyperplasia or bladder-neck obstruction.

Inhaled medicines may cause inhalation-induce bronchospasm.

As with all predominantly renally excreted drugs, Tiotropium bromide use should be monitored closely in patients with moderate to severe renal impairment (creatinine clearance of ≤ 50 mL/min).

Patients must be instructed in the correct administration of Tiotropium bromide capsules. Care must be taken not to allow the powder to enter into the eyes. Eye pain or discomfort, blurred vision, visual halos, or colored images in association with red eyes from conjunctival congestion and corneal edema may be signs of acute narrow-angle glaucoma. Should any combination of these symptoms develop specialist advice should be sought immediately.

Miotic eye drops are not considered to be effective treatment.

Tiotropium bromide should not be used more frequently than once daily.

Tiotropium bromide capsules are to be used only with the device.

PREGNANCY AND LACTATION:

Pregnancy: There is a limited amount of data from the use of Tiotropium in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity at clinically relevant doses (please refer to section Toxicology). As a precautionary measure, it is preferable to avoid the use of Tiotropium bromide during pregnancy.

Lactation: Clinical data from nursing women exposed to Tiotropium are not available. Based on lactating rodent studies, a small amount of Tiotropium is excreted into breast milk.

Therefore, Tiotropium bromide should not be used in pregnant or nursing women unless the expected benefit outweighs any possible risk to the unborn child or the infant.

Fertility: Clinical data on fertility are not available for Tiotropium. A non-clinical study performed with Tiotropium showed no indication of any adverse effect on fertility.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects on the ability to drive and use machines have been performed. The occurrence of dizziness or blurred vision may influence the ability to drive and use machinery.