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ENSIFENTRINE: AN IN-DEPTH REVIEW OF ITS THERAPEUTIC PROFILE AND THE RATIONALE FOR ITS DEVELOPMENT IN THE TREATMENT OF RESPIRATORY CONDITIONS

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ABSTRACT

Background: In order to effectively control COPD, the innovative drug ensifentrine, an inhaled PED3/4 inhibitor, improves bronchodilation and lowers inflammation. This innovative dual-mechanistic approach to COPD management sets it apart from traditional treatments that focus on just one of the mentioned mechanisms. Clinical research is being done on ensifentrine to determine how well it works to treat COPD symptoms. **Objectives:** To evaluate the efficacy of ensifentrine compared with placebo for lung function, symptoms, quality of life, and exacerbations in patients with COPD. **Methods:** The databases Embase, Cochrane Library, PubMed, and Google Scholar were used in a thorough search. The selected studies, which ranged from 2018 to 2024, examined the effects of ensifentrine on lung function, symptom alleviation, exacerbation, and quality of life through randomized controlled trials published in English. **Conclusion:** One promising medication for COPD sufferers is ensifentrine. Its combined strategy of bronchodilation and anti-inflammation enhances lung function and quality of life. Nevertheless, more investigation is still required to determine its long-term safety and generalizability to other populations.

KEYWORDS: Ensifentrine; nebulized therapy; dual PDE3 and PDE4 inhibitor, chronic obstructive pulmonary disease, clinical efficacy, drug development

INTRODUCTION

One of the most prevalent respiratory diseases, chronic obstructive pulmonary disease (COPD) affects about 380 million individuals worldwide and is responsible for about 3 million fatalities each year. Shortness of breath, persistent coughing, and sputum production are some of the symptoms of chronic obstructive pulmonary disease (COPD), a progressive illness marked by airflow restriction and persistent airway inflammation. Long-term exposure to dangerous particles, especially cigarette smoke and environmental contaminants, is one of its main causes . Airflow restriction and a gradual decline in lung function are caused by the intricate interactions of tissue damage, oxidative stress, and airway inflammation in the pathophysiology of COPD. The hunt for innovative and successful therapeutic strategies is still a crucial topic of study because of the substantial global burden of COPD.

COPD is the sixth most common cause for mortality in the US, affecting 16 million individuals.1, 2 One million ED visits and half a million hospital admissions are linked to COPD annually. An estimated $24 billion is spent on COPD-related medical expenses each year for persons 45 and older, including $6.3 billion for inpatient stays and $900 million for emergency room visits.

The main goals of current COPD treatments are symptom management, exacerbation reduction, and general quality of life enhancement. In addition to inhaled corticosteroids, bronchodilators such beta-agonists and anticholinergics are the cornerstones of pharmaceutical treatment. By lowering inflammation or relaxing the muscles in the airways, these drugs provide momentary relief. Nevertheless, a significant percentage of patients nevertheless endure unmanaged symptoms and complications in spite of the availability of these medicines, which results in hospitalizations and a worse quality of life. Alternative strategies that address both the underlying inflammation and bronchoconstriction are required, as evidenced by the diversity of COPD phenotypes and the differing reactions to current treatments.

Both pharmacological and nonpharmacological (such as cessation of smoking and pulmonary restoration) techniques may be used in treatment. Inhaled bronchodilators, particularly long-acting β-2-agonists (LABAs) and long-acting muscarinic antagonists (LAMAs), are the primary drugs used for maintenance treatment. For people with moderate to severe COPD, the 2023 Global Initiative for Chronic Obstructive Lung Disease (GOLD) principles now suggest dual combination therapy of LAMA + LABA therapy. Patients who experience

frequent exacerbations and/or have a blood eosinophil count of at least 300 cells/µl may benefit from adding inhaled corticosteroids (ICS) to their treatment plan. However, around half of COPD patients still experience everyday symptoms that affect their wellbeing even after receiving treatment.

A new therapy alternative that may help with some of the drawbacks of existing COPD medications is Ensifentrine, a novel dual inhibitor of phosphodiesterase 3 (PDE3) and phosphodiesterase 4 (PDE4). Enzymes PDE3 and PDE4 have different functions in controlling inflammatory process and smooth muscle tone in the airways, respectively. Through the simultaneous inhibition of both enzymes, Ensifentrine produces anti-inflammatory benefits through PDE4 suppression and bronchodilatory effects through PDE3 inhibition. Ensifentrine's dual mode of action sets it apart from traditional therapies, which usually concentrate on either reducing inflammation or bronchodilation but not both. Ensifentrine has therefore attracted a lot of attention as a possible game-changer in the management of COPD and other respiratory conditions.

Class of the Drug

Phosphodiesterase 3 (PDE3) inhibitor and phosphodiesterase 4 (PDE4) inhibitor

Classification

- **Phosphodiesterase 3 (PDE3) Inhibitors:** Milrinone, Cilostazol.
- **Phosphodiesterase 4 (PDE4) Inhibitors:** Roflumilast, Apremilast.

Drug description on Ensifentrine

ENSIFENTRINE (Ensifentrine) is a sterile, yellow to pale yellow aqueous inhalation suspension of Ensifentrine for oral inhalation. Ensifentrine, the active component of ENSIFENTRINE, is an inhibitor of phosphodiesterases 3 and 4 (PDE3 and PDE4). Ensifentrine has a molecular weight of 477.56 and its empirical formula is C26H31N5O4. Ensifentrine is a yellow to pale yellow crystalline powder which is practically insoluble in water. The chemical name for Ensifentrine is N-(2-{(2E)-9,10-dimethoxy-4-oxo-2-[(2,4,6-trimethylphenyl)imino]-6,7-dihydro-2H-pyrimido[6,1-a]isoquinolin-3(4H)-yl}ethyl)urea; its structural formula is:

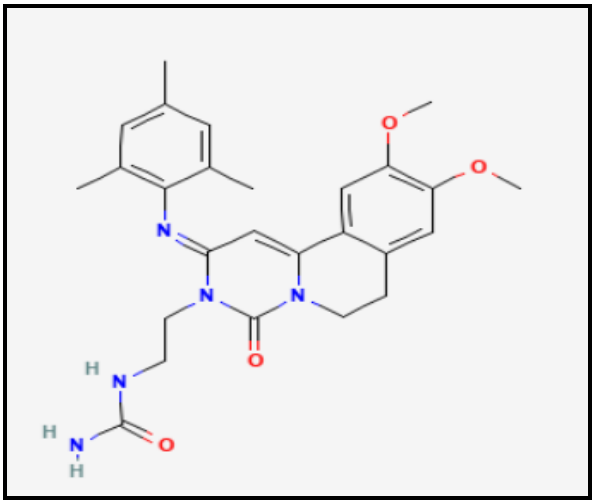

Figure - 1: Structure of Ensifentrine.

ENSIFENTRINE comes in a secured foil container with a unit-dose low-density polyethylene ampule containing 2.5 mL of sterile Ensifentrine (1.2 mg/mL) suspension. A pH 6.7 aqueous solution including dibasic sodium phosphate, monobasic sodium phosphate, polysorbate 20, sodium chloride, sorbitan monolaurate, and water for injection contains 3 mg of Ensifentrine per unit-dose ampule.

Before administering ENSIFENTRINE via nebulization, the ampule should be shaken forcefully to guarantee full resuspension of the active component. The dosage given to the lungs will vary depending on the compressor's efficiency, the nebulization system, and the patient's characteristics, just like with any other nebulized treatment.

RATIONALE FOR ENSIFENTRINE 'S DEVELOPMENT IN THE CONTEXT OF PDE3 AND PDE4 INHIBITORS

The rationale for developing ENSIFENTRINE in the presence of PDE3 and PDE4 inhibitors likely stems from a desire to enhance therapeutic outcomes in diseases where these enzymes play pivotal roles. Here's a concise overview of the reasoning.

1. Targeted Modulation of cAMP Pathways

PDE3 and PDE4 are crucial in regulating cyclic adenosine monophosphate (cAMP) levels, which influence vital physiological processes such as cardiac function, immune responses, and cognitive abilities. By developing Ensifentrine in conjunction with PDE3 and PDE4 inhibitors, researchers aim to create a more comprehensive approach to modulating cAMP pathways. This combined strategy may offer synergistic effects, potentially leading to more potent therapeutic outcomes than using individual inhibitors alone. The rationale behind this

approach is to achieve finer control over cAMP levels, allowing for more precise targeting of specific cellular processes affected by these enzymes.

Furthermore, this multi-faceted approach may help address some of the limitations associated with using PDE inhibitors individually, such as side effects or drug resistance. By carefully balancing the actions of Ensifentrine and PDE inhibitors, it may be possible to optimize treatment efficacy while minimizing adverse effects, potentially broadening the therapeutic window for various diseases involving cAMP dysregulation. Developing Ensifentrine alongside these inhibitors could allow for a more precise modulation of cAMP pathways, optimizing therapeutic effects.

2. Synergistic Therapeutic Benefits

By combining Ensifentrine with PDE3 and PDE4 inhibitors, there is potential for synergistic effects. This approach might lead to improved efficacy in managing conditions like heart failure, COPD, asthma, and certain inflammatory diseases, compared to using individual agents alone.

The combination of Ensifentrine with specific PDE inhibitors could potentially enhance the overall therapeutic strategy for conditions involving cAMP dysregulation. This synergistic approach may allow for lower doses of individual agents, potentially reducing side effects while maintaining or even improving efficacy. Furthermore, the ability to fine-tune cAMP levels through multiple mechanisms could provide more personalized treatment options, catering to individual patient needs and disease characteristics.

3. Minimization of Side Effects

Selective inhibitors of PDE3 and PDE4 have already shown promise in reducing side effects compared to non-selective inhibitors. Developing Ensifentrine in this context could further refine therapeutic interventions, offering benefits with a favorable safety profile. The combination of PDE3 and PDE4 inhibition in Ensifentrine could offer a more nuanced approach to modulating cAMP levels, potentially allowing for greater precision in targeting specific physiological processes. This tailored approach may not only enhance therapeutic outcomes but also provide clinicians with a more versatile tool for addressing complex diseases that involve multiple signaling pathways.

By leveraging the synergistic effects of dual PDE inhibition, Ensifentrine could potentially

address some of the limitations associated with single-target therapies. This approach may lead to more robust and sustained clinical responses, particularly in conditions where traditional monotherapies have shown limited efficacy or durability.

4. Broad Therapeutic Scope

PDE3 and PDE4 inhibitors are being studied for various chronic diseases. Introducing Ensifentrine might expand the therapeutic scope to new indications, providing novel treatment options. The dual inhibition mechanism of Ensifentrine could potentially offer a more comprehensive approach to managing complex diseases by targeting multiple pathways simultaneously. This strategy may not only enhance the overall therapeutic effect but also reduce the likelihood of compensatory mechanisms that often limit the efficacy of single-target therapies.

Furthermore, the broad therapeutic scope of PDE3 and PDE4 inhibitors suggests that Ensifentrine could have applications beyond its initially intended use. This versatility may open up new avenues for treating a wider range of chronic conditions, potentially revolutionizing treatment paradigms across multiple medical specialties.

5. Advancing Personalized Medicine

By understanding the specific mechanisms and interactions of Ensifentrine with PDE3 and PDE4 inhibitors, researchers can tailor treatments to individual patient needs, advancing the goals of personalized medicine.

CLINICAL PHARMACOLOGY

Mechanism of Action

Chronic respiratory tract inflammation and increasing airflow restriction are hallmarks of COPD. Each of these PDE isoforms have been determined to be potential targets in the therapeutic management of COPD because they are expressed in inflammatory cells, bronchial epithelial cells, and airway smooth muscle to promote inflammation and bronchial muscle tone. PDE3 mediates muscle tone by hydrolyzing cyclic adenosine monophosphate (cAMP), the second messenger molecule in airway smooth muscle.

Moreover, cyclic guanosine monophosphate (cGMP) can be hydrolyzed by PDE3. PDE4 exclusively controls cAMP a nd plays a role in the activation and migration of inflammatory cells as well as the stimulation of bronchial epithelial cells' Cystic Fibrosis Transmembrane

Conductance Regulator (CFTR). The PDE3 and PDE4 enzymes are specifically inhibited by the medication Ensifentrine.

PHARMACOKINETICS

Exposure to Ensifentrine increased approximately 1.4-fold greater than dose proportional following a dose 3 times the recommended dosage. By the third day after twice-daily dosing, a steady-state was achieved. Ensifentrine accumulation is predicted by population pharmacokinetic analysis to be 1.3 and 1.4 times higher for Cmax and AUC in healthy subjects and 1.4 and 1.5 times higher for Cmax and AUC in COPD subjects.

Relative bioavailability in individuals with COPD is roughly 35% lower than in healthy persons, according to population pharmacokinetic research. There was significant inter-subject variability linked to Ensifentrine exposure.

Absorption

Ensifentrine Cmax was reached approximately 0.6 to 1.5 hours after dosage in both healthy and COPD participants after inhaling the medication. The majority of an inhaled dose (about 90%) is delivered to the lung from which it is absorbed, according to a randomized, two-period, cross-over trial that evaluated systemic exposure after inhaling twice the prescribed amount of Ensifentrine with and without charcoal block. Relative bioavailability in individuals with COPD is roughly 35% lower than in healthy persons, according to population pharmacokinetic research. High inter-subject variability was linked to Ensifentrine exposure.

Half-life

Following twice-daily administration for 6 days, terminal elimination half-life ranged from 10.6 to 12.6 hours in healthy subjects and subjects with COPD (1.5 mg to 12 mg twice daily).

Distribution

Apparent central and peripheral volume of distribution for Ensifentrine in healthy subjects were 2700 L and 1820 L, respectively, as estimated in population PK analysis. In patients with COPD, apparent central and peripheral volumes were estimated as 8150 L and 5490 L, respectively.

Protein binding

In vitro plasma protein binding of Ensifentrine is approximately 90%.

Metabolism

Following administration of a single nebulized dose, 8 times the recommended dose of Ensifentrine, unchanged Ensifentrine was identified as the major drug-related component in human plasma, accounting for 96 and 99% of the drug-related material identified in Tmax and time normalized (0-24 h) plasma samples, respectively. The primary metabolic routes for Ensifentrine are oxidative (hydroxylation, O-demethylation) followed by conjugation (e.g., glucuronidation). In vitro results indicate that, at physiologically relevant concentrations, Ensifentrine was predominantly metabolized by CYP2C9 and to a lesser extent by CYP2D6.

Elimination

Following twice-daily administration for 6 days, terminal elimination half-life ranged from 10.6 to 12.6 hours in healthy subjects and subjects with COPD (1.5 mg to 12 mg twice daily)..

Excretion

The majority of Ensifentrine is excreted in feces. After a 3 mg nebulized dose, urinary elimination of unchanged Ensifentrine was negligible (<0.3% of the dose).

PHARMACODYNAMICS

Cardiac Electrophysiology

QTc interval prolongation was studied in a randomized, double-blind, placebo- and positive-controlled, 4-period crossover study in 32 healthy subjects. At 3 times the maximum recommended dose, clinically significant QTc interval prolongation was not observed.

DOSAGE AND ADMINISTRATION

Recommended Dosage

The recommended dosage of ENSIFENTRINE is 3 mg (one unit-dose ampule) twice daily, once in the morning and once in the evening, administered by oral inhalation using a standard jet nebulizer with a mouthpiece.

Toxicity

There is no information regarding the lethal dose 50 of Ensifentrine. An overdosage of Ensifentrine may lead to signs and symptoms such as headache, tachycardia, and palpitations. Treatment of overdosage consists of temporary interruption of Ensifentrine along with appropriate symptomatic and/or supportive therapy.

SAFETY MEASURES FOR APROCITENTAN USE IN PARTICULAR CATEGORIES

Pregnancy

There is insufficient information on ENSIFENTRINE use in pregnant women to assess the drug's potential to cause serious birth abnormalities, miscarriages, or other unfavorable consequences for either the mother or the fetus. Male rats given inhaled Ensifentrine at exposures 30 times the maximum recommended human daily inhalation dose (MRHDID) for 10 weeks before mating with untreated female rats resulted in higher pre- and post-implantation loss and fewer live embryos in the untreated female rats, based upon animal reproduction studies. When Ensifentrine was administered by inhalation to pregnant rats and rabbits throughout organogenesis at maternal doses up to 79 and 9 times the exposure at MRHDID, respectively, no significant birth defects were noted.

When Ensifentrine was breathed into pregnant rats from the organogenesis phase through breastfeeding at doses up to roughly 79 times the MRHDID, no negative developmental effects were seen.

It is uncertain what the specified population's estimated prior experience prevalence of serious birth abnormalities and miscarriage is. There is a background risk of birth defects, loss, or other unfavorable outcomes in every pregnancy. The estimated background risk of miscarriage and serious birth abnormalities in clinically recognized pregnancies is 15% to 20% and 2% to 4%, respectively, in the general population of the United States.

Lactation

There are no data on the presence of Ensifentrine in human milk, the effects on the breastfed child, or the effects on milk production. There are no data from animal studies on the presence of Ensifentrine in milk.

The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for ENSIFENTRINE and any potential adverse effects on the breastfed child from ENSIFENTRINE or from the underlying maternal condition.

Geriatric Use

In ENHANCE-1 and ENHANCE-2, there were 852 patients with COPD who were 65 years of age or older. In these trials, 534 (55%) of the patients randomly assigned to receive

ENSIFENTRINE were 65 years of age or older, and 84 (9%) were 75 years of age or older. Although there have been no significant variations in ENSIFENTRINE's safety or efficacy between these patients and younger adult patients, it is possible that some elderly people are more sensitive than others.

Pediatric Use

The safety and effectiveness of ENSIFENTRINE have not been established in pediatric patients.

Hepatic Impairment

Ensifentrine systemic exposure increased by 2.3-fold in subjects with moderate or severe hepatic impairment compared with healthy subjects .Use ENSIFENTRINE with caution in patients with hepatic impairment.

Renal Impairment

No dosage adjustment in patients with mild or moderate renal impairment is required. Patients with severe renal impairment have not been evaluated.

Overdosage

An overdosage of ENSIFENTRINE may lead to signs and symptoms such as headache, tachycardia,and palpitations. Treatment of overdosage consists of temporary interruption of ENSIFENTRINE along with appropriate symptomatic and/or supportive therapy.

SAFETY AND TOLERANCE CONSIDERATIONS

Acute Episodes of Bronchospasm

ENSIFENTRINE should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. ENSIFENTRINE has not been studied in the relief of acute symptoms and extra doses of ENSIFENTRINE should not be used for that purpose. The safety and effectiveness of ENSIFENTRINE for relief of acute symptoms have not been established. Acute symptoms should be treated with an inhaled, short-acting bronchodilator.

Paradoxical Bronchospasm

As with other inhaled medicines, ENSIFENTRINE may produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs following dosing with ENSIFENTRINE, it should be treated immediately with an inhaled, short-acting

bronchodilator. ENSIFENTRINE should be discontinued immediately and alternative therapy should be instituted.

Psychiatric Events Including Suicidality

An increase in psychiatric adverse effects is linked to ENSIFENTRINE treatment.

Clinical trials of individuals who received ENSIFENTRINE revealed psychiatric problems, including adverse reactions associated to suicide. A suicide-related adverse response (suicide attempt) occurred in one patient receiving ENSIFENTRINE among the pooled 24-week safety population , while a suicide-related adverse reaction (suicide) occurred in one patient receiving Ensifentrine in a different controlled study. Furthermore, among the pooled 24-week safety population, anxiety (2 patients [0.2%] ENSIFENTRINE 3 mg; 1 patient [0.2%] placebo) and insomnia (6 patients [0.6%] ENSIFENTRINE 3 mg; 2 patients [0.3%] placebo) were the most frequently reported psychiatric adverse events.

Four patients [0.4%] receiving ENSIFENTRINE experienced depression-related reactions, such as depression, major depression, and adjustment disorder with sad mood, while no patients receiving a placebo experienced any of these symptoms.

Healthcare professionals should carefully consider the risks and benefits of ENSIFENTRINE treatment before starting it for patients who have a history of depression and/or suicidal thoughts or actions. If such occurrences take place, medical professionals should carefully weigh the advantages and disadvantages of continuing ENSIFENTRINE medication.

ADVERSE REACTIONS

ENSIFENTRINE's safety was evaluated using the pooled safety population from two 24-week, double-blind, placebo-controlled trials (ENHANCE-1 and ENHANCE-2) as well as a 48-week cohort that evaluated safety in ENHANCE-1. 975 patients in all were given 3 mg of ENSIFENTRINE twice a day via oral inhalation with a standard jet nebulizer during these trials.All randomized individuals who received at least one dosage of either ENSIFENTRINE or a placebo were accounted for in the safety population.

The following list includes adverse events that were more prevalent than placebo in the pooled population and that happened at an incidence of at least 1% in ENSIFENTRINE.

8.2% of patients receiving a placebo and 7.6% of patients receiving ENSIFENTRINE stopped their medication as a result of adverse effects.

Table-1: Adverse Reactions with ENSIFENTRINE with incidence > 1% and More Common than.

Placebo in Patients with COPD in the Pooled 24-Week Safety Population (ENHANCE-1 and ENHANCE-2)

ADVERSE REACTION	ENSIFENTRINE N=975 N (%)	PLACEBO N=574 N (%)
Back pain	18 (1.8%)	6 (1.0%)
Hypertension	17 (1.7%)	5 (0.9%)
Urinary tract infection	13 (1.3%)	6 (1.0%)
Diarrhea	10 (1.0%)	4 (0.7%)

Adverse Reactions in the 48-Week Cohort

In the 48-week cohort of ENHANCE-1, 369 patients were enrolled to be treated with 3 mg ENSIFENTRINE (N=280) or placebo (N=89) twice daily for 48 weeks . The adverse reactions reported in the 48-week cohort were consistent with those observed in the pooled 24-week safety population.

Common adverse reactions

- Breathing problems that feel different or more severe than usual.
- Racing heart.
- Fever or general ill feeling.
- Swollen lymph nodes.
- Swelling of the face, lips, mouth, tongue, or throat.
- Trouble swallowing or throat tightness.
- Itching, skin rash, or pale red bumps on the skin called hives.
- Nausea or vomiting.
- Dizziness, feeling lightheaded, or fainting.
- Stomach cramps.
- Joint pain.
- New or increased thoughts of suicide or death.
- Suicide attempt.
- New or increased feelings of anxiety, depression, or other unusual changes in mood or behavior.

CONTRAINDICATIONS

ENSIFENTRINE is contraindicated in patients with hypersensitivity to Ensifentrine or any component of this product.

DRUG INTERACTION STUDIES

Effect of Other Drugs on ENSIFENTRINE

Clinical Studies

Ensifentrine and Cytochrome P450: Ensifentrine Cmax and AUC0-inf were 1.4-fold and 1.6-fold higher; respectively, when a 3 mg single dose of ENSIFENTRINE was concomitantly administered with CYP2C9 inhibitor fluconazole (200 mg twice daily).

In Vitro Studies

Ensifentrine and Efflux Transporters: Ensifentrine is not a substrate of the efflux transporter P-glycoprotein (P-gp). Ensifentrine is a substrate of breast cancer resistance protein (BCRP). Ensifentrine and Uptake Transporters: Ensifentrine is not a substrate of the uptake transporters OATP1B1 or OATP1B3.

Effect of ENSIFENTRINE on Other Drugs

In Vitro Studies

Ensifentrine and Cytochrome P450: At therapeutically relevant concentrations, Ensifentrine does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4.

Ensifentrine and Efflux Transporters: At therapeutically relevant concentrations, Ensifentrine is not an inhibitor of either BCRP or P-gp.

Ensifentrine and Uptake Transporters: Ensifentrine does not inhibit the transporters, OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1 or MATE2-K, at therapeutically relevant concentrations.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

A two-year inhalation study in Han Wistar rats and a 6-month oral study in Tg.rasH2 transgenic mice were conducted to assess the carcinogenic potential of Ensifentrine. No evidence of tumorigenicity was observed in male and female rats at an exposure approximately 40 times the MRHDID. No evidence of tumorigenicity was observed in male

and female Tg.rasH2 mice at oral doses up to 80 mg/kg/day, the highest dose tested.

Ensifentrine was negative for genotoxicity in the following assays: in vitro Ames test for bacterial gene mutation, in vivo comet test with rats, or in vivo micronucleus assay with mice.

In a male fertility study, Ensifentrine was administrated to male rats at inhalation doses of 2, 6, and 16 mg/kg/day (4, 13, and 30 times the exposure at the MRHDID) for 10 weeks prior to mating to untreated females. Male rats had decreased sperm motility and increased abnormal sperm morphology at an inhalation dose of 16 mg/kg/day (approximately 30 times the exposure at the MRHDID). Decreased sperm counts in the testis were observed at all doses. Atrophy/degeneration in the testis and intraluminal germ cell debris in the epididymis were observed at doses of 6 (13 times the exposure at the MRHDID) and 16 mg/kg/day (30 times the exposure at the MRHDID). Additional adverse effects at 16 mg/kg/day on reproductive performance included decreased mating index and decreased fertility index. The sperm counts, sperm motility, and sperm morphology were reversible at the end of a 4-week treatment-free period. Atrophy/degeneration in the testis and intraluminal germ cell debris in the epididymis were not present at the end of a 4-week treatment-free period.

In a female fertility study, Ensifentrine was administrated to female rats at inhalation doses of up to 18 mg/kg/day from two weeks prior to mating to 7 days after mating. Ensifentrine had no effect on female fertility and reproductive performance indices up to 18 mg/kg/day (31 times the exposure at the MRHDID).

INDICATIONS

Ensifentrine, RPL554, is an inhaled bifunctional dual phosphodiesterase 3/4 inhibitor with both bronchodilator and anti-inflammatory activities, offering new options in treating COPD and other inflammatory airway diseases currently under clinical scrutiny.

Ensifentrine, is primarily indicated for the maintenance treatment of chronic obstructive pulmonary disease (COPD) in adults. Here are some detailed indications and considerations:

COPD Maintenance: Ensifentrine is used as a long-term treatment to manage COPD symptoms, helping to reduce inflammation and improve airflow.

Dual Mechanism: As a dual inhibitor of phosphodiesterase 3 (PDE3) and phosphodiesterase

4 (PDE4), it provides both bronchodilation and anti-inflammatory effects.

Non-Steroidal Option: It offers a non-steroidal approach to COPD management, which is beneficial for patients who may not respond well to existing treatments.

Potential for Other Conditions: While its primary indication is for COPD, ensifentrine is being explored for other respiratory conditions such as asthma, cystic fibrosis, and bronchiectasis due to its unique mechanism of action.

CONCLUSION

Inhaled phosphodiesterase inhibitors are not yet approved for use as maintenance treatment for chronic obstructive pulmonary disease (COPD). When used alone or in conjunction with standard of care, ensifentrine has demonstrated encouraging outcomes in phase III clinical trials (the ENHANCE trials) in terms of improved lung function, better symptom control, possible reduction in exacerbations, and no increased side effects. For patients receiving maximal therapy with medications such as oral antibiotics, oral PDE4 inhibitors, inhaled bronchodilators, or inhaled corticosteroids, ensifentrine in an inhalational nebulized formulation exhibits potential as a novel maintenance treatment.

The US Food and Drug Administration is now reviewing this treatment, and a decision is scheduled in 2024. Because of its robust clinical profile, minimal adverse effects, and general high tolerance, ensifentrine has great promise as an adjunct to the existing COPD protocol of treatment. Additionally, it can be a treatment that limits some patients' interaction with bronchodilators or inhaled steroids.

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