



GSK Announces Positive EU Approval for Labelling Update to Relvar Ellipta in Patients with Asthma

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LONDON & BRISBANE, Calif.--(BUSINESS WIRE)--Mar. 8, 2018-- GlaxoSmithKline plc (LSE/NYSE:GSK) and Innoviva, Inc. (NASDAQ: INVA) today announced that the European Commission has approved a label update for the use of once-daily Relvar Ellipta (fluticasone furoate/vilanterol, FF/VI), an inhaled corticosteroid (ICS) / long-acting β_2 -agonist (LABA) combination, in patients whose asthma is already adequately controlled on both an inhaled corticosteroid and long-acting β_2 -agonist.

The Type II variation regulatory approval has been supported by data from a non-inferiority lung function study, which demonstrated that patients with adequately controlled asthma were able to switch to the once-daily FF/VI 100/25, from the twice-daily Seretide Accuhaler (fluticasone propionate /salmeterol, FP/SAL) 250/50, without compromising their lung function. No new safety signals were identified and the adverse event data were consistent with the known safety profile for FF/VI established in patients with asthma.

Jonathan Sweeting, SVP and Head of Global Respiratory Franchise GSK, said: "Patients with asthma can continue to experience symptoms despite being adequately controlled and these symptoms can impact their lives. This label update gives doctors the option of switching appropriate patients from their current ICS/LABA to once-daily Relvar Ellipta."

Dr. Theodore J. Witek Jr., Senior Vice President and Chief Scientific Officer of Innoviva, Inc., added: "The evidence supporting this regulatory update means doctors can be confident that patients taking once-daily Relvar Ellipta will experience comparable benefit in lung function and safety profile, as with a twice-daily ICS/LABA. We welcome this approval, which signifies an important milestone for Relvar Ellipta."

The updated marketing authorisation by the European Commission will be reflected in the label for Relvar Ellipta for countries in the European Union.

About asthma

Asthma is a chronic lung disease that inflames and narrows the airways. Asthma affects 358 million people worldwide. Despite medical advances, more than half of patients continue to experience poor control and significant symptoms impacting their daily life.

The causes of asthma are not completely understood but likely involve an interaction between a person's genetic make-up and the environment. Key risk factors are inhaled substances that provoke allergic reactions or irritate the airways.

About Relvar Ellipta (fluticasone furoate + vilanterol)

Relvar Ellipta is a once-daily dual combination treatment comprising fluticasone furoate, an inhaled corticosteroid and vilanterol, a long-acting β_2 -agonist, in a single inhaler, the Ellipta[®].

Relvar Ellipta is indicated in Europe for the regular treatment of asthma in adults and adolescents aged 12 years and older where use of a combination medicinal product (long-acting β_2 -agonist, and inhaled corticosteroid) is appropriate: patients not adequately controlled with inhaled corticosteroids and 'as-needed' inhaled short acting β_2 -agonists; patients already adequately controlled on both inhaled corticosteroid and long-acting β_2 -agonist.

Full EU prescribing information is available at: [EU Prescribing Information for Relvar Ellipta](#).

GSK's commitment to respiratory disease

GSK has led the way in developing innovative medicines to advance the management of asthma and COPD for nearly 50 years. Over the last four years we have launched six innovative medicines responding to continued unmet patient need, despite existing therapies. This is an industry leading portfolio in breadth, depth and innovation, developed to reach the right patients, with the right treatment.

We remain at the cutting-edge of scientific research into respiratory medicine, working in collaboration with patients and the scientific community to offer innovative medicines aimed at helping to treat patients' symptoms and reduce the risk of their disease worsening. While respiratory diseases are clinically distinct, there are important pathophysiological features that span them, and our ambition is to have the most comprehensive portfolio of medicines to address a diverse range of respiratory diseases. To achieve this, we are focusing on targeting the underlying disease-driving biological processes to develop medicines with applicability across multiple respiratory diseases. This approach requires extensive bioinformatics, data analytic capabilities, careful patient selection and stratification by phenotype in our clinical trials.

Important safety information for Relvar Ellipta in Europe

FF/VI is contraindicated in patients with hypersensitivity to either fluticasone furoate, vilanterol, or any of the excipients.

FF/VI should not be used to treat acute asthma symptoms or an acute exacerbation in COPD, for which a short-acting bronchodilator is required. Increasing use of short-acting bronchodilators to relieve symptoms indicates deterioration of control and patients should be reviewed by a physician.

Patients should not stop therapy with FF/VI in asthma or COPD, without physician supervision since symptoms may recur after discontinuation.

Asthma-related adverse events and exacerbations may occur during treatment with FF/VI. Patients should be asked to continue treatment but to seek medical advice if asthma symptoms remain uncontrolled or worsen after initiation of treatment with FF/VI.

Paradoxical bronchospasm may occur with an immediate increase in wheezing after dosing. This should be treated immediately with a short-acting inhaled bronchodilator. FF/VI should be discontinued immediately, the patient assessed and alternative therapy instituted if necessary.

Cardiovascular effects, such as cardiac arrhythmias e.g. supraventricular tachycardia and extrasystoles may be seen with sympathomimetic medicinal products including FF/VI. Therefore fluticasone furoate/vilanterol should be used with caution in patients with severe cardiovascular disease.

For patients with moderate to severe hepatic impairment, the 92/22 mcg dose should be used and patients should be monitored for systemic corticosteroid-related adverse reactions. FF/VI 184/22 mcg is not indicated for patients with COPD. There is no additional benefit of the 184/22 mcg dose compared to the 92/22 mcg dose and there is a potential increased risk of pneumonia and systemic corticosteroid-related adverse reactions.

An increase in the incidence of pneumonia has been observed in subjects with COPD receiving FF/VI. There was also an increased incidence of pneumonias resulting in hospitalisation. In some instances these pneumonia events were fatal.

The incidence of pneumonia in patients with asthma was common at the higher dose. In a previous study of FF/VI in asthma the incidence of pneumonia in patients with asthma taking FF/VI 184/22 mcg was numerically higher compared with those receiving FF/VI 92/22 mcg or placebo.

Hyperglycaemia: There have been reports of increases in blood glucose levels in diabetic patients and this should be considered when prescribing to patients with a history of diabetes mellitus.

Systemic effects may occur with any inhaled corticosteroid, particularly at high doses prescribed for long periods. These effects are much less likely to occur than with oral corticosteroids. Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression, decrease in bone mineral density, growth retardation in children and adolescents, cataract and glaucoma and more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children).

FF/VI should be administered with caution in patients with pulmonary tuberculosis or in patients with chronic or untreated infections. Data from large asthma and COPD clinical trials were used to determine the frequency of adverse reactions associated with FF/VI.

Very common adverse reactions (occurring in >1/10 patients) with FF/VI were headache and nasopharyngitis. Common adverse reactions (occurring in >1/100 to <1/10 patients) were pneumonia, upper respiratory tract infection, bronchitis, influenza, candidiasis of mouth and throat, oropharyngeal pain, sinusitis, pharyngitis, rhinitis, cough, dysphonia, abdominal pain, arthralgia, back pain, fractures, and pyrexia and muscle spasms. Extrasystoles were observed as an uncommon adverse reaction (occurring in >1/1,000 to <1/100 patients). Rare adverse reactions (occurring in >1/10,000 to <1/1,000) were hypersensitivity reactions (including anaphylaxis, angioedema, rash and urticaria), anxiety, tremor, palpitations, tachycardia and paradoxical bronchospasm. With the exception of pneumonia and fractures, the safety profile was similar in patients with asthma and COPD. During clinical studies, pneumonia and fractures were more frequently observed in patients with COPD.

Relvar Ellipta is known as Breo Ellipta in the United States.

Full US prescribing information is available at us.gsk.com or [US Prescribing Information for Breo Ellipta](#).

About Seretide Accuhaler (fluticasone propionate + salmeterol)

Seretide Accuhaler is a twice-daily dual combination treatment comprising fluticasone propionate /salmeterol, in the Accuhaler inhaler.

Seretide Accuhaler is indicated in Europe in the regular treatment of patients aged 4 and over with asthma, where use of a combination product (long-acting β_2 -agonist, LABA, and inhaled corticosteroid, ICS) is appropriate: Patients not adequately controlled on both ICS and 'as-needed' short-acting β_2 -agonist (SABA); Patients already adequately controlled on both ICS and LABA.

For the UK Summary of Product Characteristics (SmPC), please visit: <https://www.medicines.org.uk/emc/medicine/2317/SPC/Seretide+100,+250,+500+Accuhaler>

Important safety information for Seretide Accuhaler

Uses: Asthma: Regular treatment of asthma, where a long-acting β_2 agonist and inhaled corticosteroid is appropriate, i.e. patients uncontrolled on inhaled corticosteroids and 'as needed' short-acting inhaled bronchodilator or patients controlled on inhaled corticosteroid and long-acting β_2 agonist. Lowest strength Seretide (salmeterol 25mcg/fluticasone propionate 50 mcg and salmeterol 50mcg/fluticasone propionate 100 mcg) not appropriate in severe asthma. COPD: Symptomatic treatment of patients with COPD with a FEV1 <60% predicted normal (pre-bronchodilator) and a history of repeated exacerbations, who have significant symptoms despite regular bronchodilator therapy.

Dosage and administration: Inhalation only. Asthma: *Adults and adolescents 12 years and over:* Seretide Accuhaler - one inhalation b.d. of: Seretide 100 (salmeterol 50 mcg/fluticasone propionate 100 mcg) or Seretide 250 (salmeterol 50 mcg/fluticasone propionate 250 mcg) or Seretide 500 (salmeterol 50 mcg/fluticasone propionate 500 mcg), Seretide Evohaler – two puffs b.d. of: Seretide 50 (salmeterol 25 mcg/fluticasone propionate 50 mcg) or Seretide 125 (salmeterol 25 mcg/fluticasone propionate 125mcg) or Seretide 250 (salmeterol 25 mcg/fluticasone propionate 250 mcg). *Children 4-11 years:* Seretide 50 Evohaler (salmeterol 25 mcg/fluticasone propionate 50 mcg): two puffs b.d. Spacer recommended for co-ordination. Seretide 100 Accuhaler (salmeterol 50 mcg/fluticasone propionate 100 mcg) one inhalation b.d. Regularly review patients and reduce dose to lowest that maintains effective symptom control. Where the control of symptoms is maintained with the lowest strength of the combination, patients may be prescribed an inhaled corticosteroid alone, or if a long-acting β_2 agonist is required, Seretide may be given once daily. If rapid control of asthma in adults or adolescents with moderate persistent asthma (defined as patients with daily symptoms, daily rescue use and moderate to severe airflow limitation) is essential, an initial dose of two inhalations b.d of Seretide 50 Evohaler (salmeterol 25 mcg/fluticasone propionate 50 mcg) or one inhalation b.d of Seretide 100 Accuhaler (salmeterol 50 mcg/fluticasone propionate 100 mcg) may be considered on a short-term basis. Once control of asthma is attained treatment should be regularly reviewed and stepped down. Doubling the dose of all strengths of Seretide may be considered when adult patients require additional short-term (up to 14 days) inhaled corticosteroid therapy but this causes a small increase in β_2 -agonist-related adverse events. COPD: one inhalation b.d. of Seretide 500 Accuhaler (salmeterol 50mcg/fluticasone propionate 500 mcg).

Contraindications: Hypersensitivity to the active ingredients or to any of the excipients.

Precautions: Pulmonary tuberculosis, fungal, viral or other infections of the airway, severe cardiovascular disorders, heart rhythm abnormalities, diabetes mellitus, hypokalaemia and thyrotoxicosis. Increased reporting of pneumonia and bronchitis in patients with COPD receiving Seretide compared with placebo. If a patient with severe COPD has experienced pneumonia, treatment with Seretide should be re-evaluated. Paradoxical bronchospasm post dose. *Severe/unstable asthma:* Warn patients to seek medical advice if short-acting inhaled bronchodilator use increases. Consider increased inhaled/additional corticosteroid therapy. *Acute symptoms:* Not for acute symptoms. Use short-acting inhaled bronchodilator. *Systemic effects:* Systemic effects of inhaled corticosteroids may occur, particularly at high doses for prolonged periods, but much less likely than with oral corticosteroids. May include Cushing's syndrome, cushingoid features, adrenal suppression, adrenal crisis, growth retardation in children and adolescents, decrease in bone mineral density, cataract, glaucoma and, more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children). Monitor height of children on prolonged inhaled corticosteroid therapy. Tremor, palpitations and headache, have been reported with β_2 agonist treatment. In asthma, therapy should be down titrated under physician supervision to lowest effective dose and treatment should not be abruptly stopped due to risk of exacerbation. Serious asthma-related adverse events and exacerbations may occur during treatment with Seretide. Patients should not be initiated on Seretide during an exacerbation, or if they have significantly worsening or acutely deteriorating asthma. Data from a large asthma trial suggested patients of black African or Afro-Caribbean ancestry were at increased risk of serious respiratory-related events or deaths when using salmeterol. All patients should continue treatment but seek medical advice if asthma symptoms remain uncontrolled or worsen when initiated on Seretide or using Seretide. In COPD cessation of therapy may also be associated with decompensation and should be supervised by a physician. *Transfer from oral steroids:* Special care needed. Consider appropriate steroid therapy in stressful situations.

Drug interactions: Avoid beta-blockers. Avoid concomitant administration of ketoconazole or other potent (e.g. itraconazole, telithromycin, ritonavir) and moderate (erythromycin) CYP3A4 inhibitors unless benefits outweigh potential risk. β_2 adrenergic blockers may weaken or antagonise the effect of salmeterol. Potentially serious hypokalaemia may result from β_2 agonist therapy. Particular caution is advised in acute severe asthma as this effect may be potentiated by concomitant treatment with xanthine derivatives, steroids and diuretics.

Pregnancy and lactation: Experience limited. Balance risks against benefits.

Side effects: *Very Common:* headache, nasopharyngitis. *Common:* candidiasis of the mouth and throat, hoarseness/dysphonia, throat irritation, pneumonia, bronchitis, hypokalaemia, sinusitis, contusions, traumatic fractures, arthralgia, myalgia, muscle cramps. *Uncommon:* respiratory symptoms (dyspnoea), anxiety, tremor, palpitations, tachycardia, angina pectoris, atrial fibrillation, cutaneous hypersensitivity reactions, hyperglycaemia, sleep disorders, cataract. *Rare:* angioedema, respiratory symptoms (bronchospasm), anaphylactic reactions including anaphylactic shock, Cushing's syndrome, cushingoid features, adrenal suppression, growth retardation in children and adolescents, decreased bone mineral density, oesophageal candidiasis, behavioural changes including psychomotor hyperactivity and irritability (predominately in children), glaucoma, cardiac arrhythmias and paradoxical bronchospasm. *Not known:* depression or aggression (particularly in children). *Paradoxical bronchospasm:* substitute alternative therapy.

Seretide Accuhaler is known as ADVAIR DISKUS in the United States.

Full US prescribing information, is available at us.gsk.com or [US Prescribing Information for Advair Diskus](#).

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Innoviva – Innoviva is focused on bringing compelling medicines to patients in areas of unmet need by leveraging its significant expertise in the development, commercialization and financial management of bio-pharmaceuticals to maximize the potential of its respiratory assets partnered with Glaxo Group Limited (GSK), including RELVAR®/BREO® ELLIPTA®, ANORO® ELLIPTA®, and TRELEGY® ELLIPTA®. Under the agreement with GSK, Innoviva is eligible to receive associated royalty revenues from RELVAR®/BREO® ELLIPTA®, and ANORO® ELLIPTA®. In addition, Innoviva retains a 15 percent economic interest in future payments made by GSK for earlier-stage programs partnered with Theravance Biopharma, Inc., including TRELEGY® ELLIPTA®. For more information, please visit Innoviva's website at www.inva.com.

Cautionary statement regarding forward-looking statements

GSK cautions investors that any forward-looking statements or projections made by GSK, including those made in this announcement, are subject to risks and uncertainties that may cause actual results to differ materially from those projected. Such factors include, but are not limited to, those described under Item 3.D 'Principal risks and uncertainties' in the company's Annual Report on Form 20-F for 2016.

Innoviva forward-looking statements

This press release contains certain "forward-looking" statements as that term is defined in the Private Securities Litigation Reform Act of 1995 regarding, among other things, statements relating to goals, plans, objectives and future events, including the development, regulatory and commercial plans for Relvar Ellipta. Innoviva intends such forward-looking statements to be covered by the safe harbor provisions for forward-looking statements contained in Section 21E of the Securities Exchange Act of 1934 and the Private Securities Litigation Reform Act of 1995. Such forward-looking statements involve substantial risks, uncertainties and assumptions. These statements are based on the current estimates and assumptions of the management of Innoviva as of the date of this press release and are subject to risks, uncertainties, changes in circumstances, assumptions and other factors that may cause the actual results of Innoviva to be materially different from those reflected in the forward-looking statements. Important factors that could cause actual results to differ materially from those indicated by such forward-looking statements are described under the headings "Risk Factors" and "Management's Discussion and Analysis of Financial Condition and Results of Operations" contained in Innoviva's Annual Report on Form 10-K for the year ended December 31, 2017, which is on file with the U.S. Securities and Exchange Commission (SEC) and available on the SEC's website at www.sec.gov. In addition to the risks described above and in Innoviva's other filings with the SEC, other unknown or unpredictable factors also could affect Innoviva's results. No forward-looking statements can be guaranteed and actual results may differ materially from such statements. Given these uncertainties, you should not place undue reliance on these forward-looking statements. The information in this press release is provided only as of the date hereof, and Innoviva assumes no obligation to update its forward-looking statements on account of new information, future events or otherwise, except as required by law. (INVA-G).

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