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Summary of the risk management plan (RMP) for Vylaer Spiromax (budesonide / formoterol)

This is a summary of the risk management plan (RMP) for Vylaer Spiromax, which details the measures to be taken in order to ensure that Vylaer Spiromax is used as safely as possible. For more information on RMP summaries, see here.

This RMP summary should be read in conjunction with the EPAR summary and the product information for Vylaer Spiromax, which can be found on Vylaer Spiromax's EPAR page.

Overview of disease epidemiology

Vylaer Spiromax is used in adults to treat asthma and severe chronic obstructive pulmonary disease (COPD).

Asthma

Asthma is a common, life-long inflammatory disease of the airways that affects children and adults of all ages. It is one of the most common chronic diseases worldwide, and can be life-threatening. Symptoms come and go and include shortness of breath, wheezing, chest tightness and cough. The cause of asthma is unknown; however, a family history of asthma, eczema or allergy makes it more likely that an individual will develop asthma.

Estimates of the prevalence in European countries range from around 10 to 13% in the UK to 0.28% in Georgia. There is evidence that its prevalence has considerably increased in recent years, especially in children. Across the world, the number of deaths related to asthma is estimated at around 250,000 per year.

Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) is a long-term disease in which the airways and air sacs inside the lungs become damaged or blocked, leading to difficulty breathing. Symptoms of COPD usually develop over a number of years and can include breathlessness (especially after physical activity), persistent cough sometimes with mucus, wheezing, and frequent chest infections. The main cause is smoking, but other factors have been identified. The disease is aggravated by bacterial and viral infections which cause exacerbations (flare-ups). Exacerbations and chest infections can lead to hospital admissions and in some cases can be fatal.

It is estimated that there are around 210 million people with COPD worldwide. Males are more often affected than females, and Europeans are more often affected than Asians and particularly more than Africans. Generally, COPD becomes more common with increasing age. Less than 6% of people between the ages of 25 and 44 years suffer from mild and moderate COPD, while more than 40% of people aged 75 years and older suffer from mild and moderate COPD.

Summary of treatment benefits

Vylaer Spiromax contains two active substances, budesonide and formoterol:

- budesonide belongs to a group of medicines called 'corticosteroids'. It works by reducing and preventing swelling and inflammation in the lungs.
- formoterol belongs to a group of medicines called 'long-acting beta$_2$-adrenoceptor agonists' (LABAs) or 'bronchodilators'. It works by relaxing the muscles in the airways. This helps to breathe more easily.

Vylaer Spiromax is a 'hybrid medicine'. This means that it is similar to a 'reference medicine' containing the same active substances, but Vylaer Spiromax is given using a different inhaler. Because Vylaer Spiromax is a hybrid medicine, its benefits and risks are taken as being the same as those of Symbicort Turbohaler, the reference medicine. Studies in patients have been limited to tests to determine that Vylaer Spiromax is bioequivalent to the reference medicine (two medicines are bioequivalent when they produce the same levels of the active substance in the body). Clinical studies have shown that the addition of formoterol to budesonide improved symptoms and lung function, and reduced exacerbations with asthma and COPD.

Unknowns relating to treatment benefits

Vylaer Spiromax has not been studied in children or adolescents under the age of 18 years. There are no data available for use of budesonide/formoterol in patients with reduced liver and kidney function.

Summary of safety concerns

Important identified risks

Risks	What is known	Preventability
Systemic glucocorticosteroid effects (systemic means that the medicine is carried throughout the body in the bloodstream from the site of application and have general rather than only local effects)	Budesonide is a glucocorticosteroid and shares the actions of this class of hormones. Corticosteroids used at high doses for a long time can lead to the following: • changes in bone mineral density (thinning of the bones); • cataract (clouding of the lens in the eye); • glaucoma (high pressure in the eye); • a slowing of the rate of growth of children and adolescents; • an effect on the adrenal gland (a small gland next to the kidney); • restlessness, nervousness or	Budesonide/formoterol should be used exactly as instructed by a doctor or pharmacist. Patients should check with their doctor or pharmacist if they are not sure. Patients should talk to their doctor or pharmacist before using budesonide/formoterol if they have problems with the thyroid or adrenal glands. Patients should tell their doctor or pharmacist if they are taking steroid medicines taken by mouth (such as prednisolone). If patients have been taking steroid tablets for asthma or COPD, the doctor may reduce the number of tablets being taken when treatment with budesonide/formoterol is started. If patients have been taking oral steroid

	agitation; • disturbed sleep; • bruising of the skin; • depression; • changes in behaviour, especially in children. These effects are much less likely to happen with inhaled corticosteroids than with corticosteroid tablets.	tablets for a long time, the doctor may carry out blood tests from time to time. The doctor may consider adding steroid tablets to the usual treatment during periods of stress (for example, during a chest infection or before an operation).
Heart problems due to formoterol (which belongs to a class of medicines called long-acting adrenergic beta 2 receptor agonists or LABAs)	Formoterol is a LABA and shares the actions of this class of 'bronchodilators'. Palpitations (awareness of the heart beating) have been reported commonly with budesonide/formoterol (affecting less than 1 in 10 people), fast heartbeat uncommonly (affecting less than 1 in 100 people), chest pain or tightness in the chest (angina pectoris) very rarely (affecting less than 1 in 10,000 people), and uneven heart beat rarely (may affect up to 1 in 1,000 people).	Patients should talk to their doctor or pharmacist before using budesonide/formoterol if they have: • high blood pressure, or have ever had a heart problem (including an uneven heartbeat, a very fast pulse, narrowing of the arteries or heart failure); • problems with the thyroid or adrenal glands; • low levels of potassium in the blood. Patients should tell their doctor or pharmacist if they are taking any of the following medicines: • medicines for a fast or uneven heart beat (such as quinidine, disopyramide and procainamide); • medicines like digoxin, often used to treat heart failure; • tricyclic antidepressants (such as amitriptyline) and the antidepressant nefazodone; • medicines called monoamine oxidase inhibitors (such as phenelzine, furazolidone and procarbizine); • phenothiazine medicines (such as chlorpromazine); • medicines for Parkinson's disease (such as levodopa);

		• medicines for thyroid problems (such as levothyroxine); • medicines for allergies or antihistamines (such as terfenadine); • diuretics, also known as 'water tablets' (such as furosemide), used to treat high blood pressure; • steroid medicines taken by mouth (such as prednisolone); • xanthine medicines (such as theophylline or aminophylline),often used to treat asthma; • other bronchodilators (such as salbutamol). The levels of potassium in the blood may be monitored if patients suffer from unstable asthma with variable use of rescue bronchodilators, from acute severe asthma or from other conditions associated with low potassium levels.
Life-threatening and fatal asthma events with long-acting adrenergic beta 2 receptor agonists (LABAs)	Serious asthma-related adverse events and exacerbations may occur during treatment.	If asthma symptoms remain uncontrolled or worsen after initiating therapy with budesonide/formoterol, patients should continue treatment and see their doctor as soon as possible.
A sudden temporary narrowing of the airways (paradoxical bronchospasm)	As with other inhalation therapies, a paradoxical bronchospasm can occur with budesonide/formoterol, causing an immediate increase in wheezing, shortness of breath and cough after dosing. Paradoxical bronchospasm was reported very rarely in patients taking budesonide/formoterol (may affect up to 1 in 10,000 people).	If symptoms occur, patients should stop using budesonide/formoterol straight away and use their "reliever" inhaler. They should also contact their doctor immediately as they may need to have their treatment changed.
Low blood levels of potassium (hypokalaemia) which can cause muscle weakness, twitching or	Low levels of potassium in the blood have been reported rarely (may affect up to 1 in 1,000 people) in patients taking budesonide/formoterol.	Patients should talk to their doctor or pharmacist before using budesonide/formoterol if they have low levels of potassium in the blood. Patients should tell their doctor or

abnormal heart rhythm		pharmacist if they are taking any medicines that can lower the amount of potassium in the blood: • diuretics, also known as 'water tablets' (such as furosemide). These are used to treat high blood pressure. • steroid medicines that are taken by mouth (such as prednisolone). • xanthine medicines (such as theophylline or aminophylline). These are often used to treat asthma. • other bronchodilators (such as salbutamol). Patients should tell their doctor if they experience muscle weakness, twitching or abnormal heart rhythm. The levels of potassium in the blood may be monitored if patients suffer from unstable asthma with variable use of rescue bronchodilators, from acute severe asthma or from other conditions associated with low potassium levels.

Important potential risks

Risks	**What is known**
Off-label use in children and adolescents under 18 years (unlicensed use of medicine)	Vylaer Spiromax should not be used in children and adolescents under the age of 18 years. The risk of off-label use arises from the fact that the reference product Symbicort Turbohaler is approved for treatment of asthma as a maintenance therapy in children 6 years and older.
Potential for off-label use of the highest strength (320/9.0) of budesonide/formoterol in the "maintenance and reliever therapy regimen"	Vylaer Spiromax 320/9 micrograms (mcg) should not be used as a reliever inhaler. There is a potential safety concern if the 320/9.0 mcg strength is used to substituted directly for the 160/4.5 mcg strength, given the recommended maximum number of daily inhalations (12) with the maintenance and reliever approach. If the highest strength were used this way, this would expose patients to a high dose of budesonide and formoterol.
Simultaneous use with medicines called 'beta-adrenergic blockers' and 'strong	Budesonide/formoterol may interact with certain medicines that are potent inhibitors of CYP3A4: • medicines to treat infections (e.g. ketoconazole, itraconazole,

inhibitors of CYP3A4'	voriconazole, posaconazole, clarithromycin and telithromycin); • medicines called 'HIV-protease inhibitors' (e.g. ritonavir) to treat HIV infection; • the anti-depressant nefazodone. These medicines are likely to markedly increase blood levels of budesonide and potentially induce systemic glucocorticosteroid effects of budesonide/formoterol. Beta-blocker medicines (such as atenolol or propranolol used to treat high blood pressure), including eye drops (such as timolol for glaucoma), may weaken or inhibit the effect of formoterol and therefore of budesonide/formoterol as well. Patients should tell their doctor or pharmacist if they are taking, have recently taken or might take any other medicines.

Missing information

Risk	**What is known**
Use in pregnant or breastfeeding women	There are no data from studies with budesonide/formoterol in pregnant women. During pregnancy, budesonide/formoterol should only be used when the benefits outweigh the potential risks. Budesonide passes into breast milk. It is not known whether formoterol passes into human breast milk. Use of budesonide/formoterol in women who are breastfeeding should only be considered if the expected benefit to the mother is greater than any possible risk to the child.
Use in patients with reduced kidney function	There are no data available on the use of Vylaer Spiromax in patients with reduced kidney function.
Use in patients with reduced liver function	There are no data available on the use of Vylaer Spiromax in patients with reduced liver function. As budesonide and formoterol are mostly broken down in the liver, patients with severe liver problems (e.g. severe liver cirrhosis) may be exposed to higher levels of these medicines.
Use in children and adolescents	The safety and efficacy of Vylaer Spiromax in children and adolescents has not yet been established.

Summary of risk minimisation measures by safety concern

All medicines have a summary of product characteristics (SmPC) which provides physicians, pharmacists and other healthcare professionals with details on how to use the medicine, and also describes the risks and recommendations for minimising them. Information for patients is available in lay language in the package leaflet. The measures listed in these documents are known as 'routine risk minimisation measures'.

The SmPC and the package leaflet are part of the medicine's product information. The product information for Vylaer Spiromax can be found on Vylaer Spiromax's EPAR page.

This medicine has no additional risk minimisation measures.

Planned post-authorisation development plan

List of studies in post-authorisation development plan

Study / activity (including study number)	***Objectives***	***Safety concerns / efficacy issue addressed***	***Status***	***Planned date for submission of (interim and) final results***
A paediatric / adolescent pharmacokinetic study (a study of what happens to the drug in the body, including its movement and its metabolism)	To demonstrate that the pharmacokinetic and safety profile of budesonide/formoterol (80/4.5 mcg) is comparable with the reference product Symbicort Turbohaler (100/6 mcg)	Pharmacokinetic and safety profiles of budesonide/formoterol (80/4.5 mcg) in mild asthmatic children and adolescents is not yet determined	Planned (start of the study is anticipated for Q4 2014)	Not available

Studies which are a condition of the marketing authorisation

None

Summary of changes to the risk management plan over time

Not applicable

This summary was last updated in 10-2014.