EMA/682063/2014

Summary of the risk management plan (RMP) for Brimica Genuair (aclidinium / formoterol fumarate dihydrate)

This is a summary of the risk management plan (RMP) for Brimica Genuair, which details the measures to be taken in order to ensure that Brimica Genuair 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 Brimica Genuair, which can be found on Brimica Genuair's EPAR page.

Overview of disease epidemiology

Brimica Genuair is a medicine used to relieve the symptoms of chronic obstructive pulmonary disease (COPD) in adults. 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 of COPD is smoking. The disease is aggravated by bacterial and viral chest infections which cause exacerbations (flare-ups). Both exacerbations and chest infections can require admission to hospital and in some cases can lead to death.

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

Summary of treatment benefits

Brimica Genuair contains two active substances called aclidinium bromide and formoterol fumarate dihydrate, which work by keeping the airways open and allowing the patient to breathe more easily. The two active substances are delivered directly into the lungs by a dry powder inhaler.

One active substance, aclidinium bromide, is a 'long-acting muscarinic antagonist' (LAMA) and the other, formoterol fumarate dihydrate, is a 'long-acting beta2 agonist' (LABA). Both classes of medicines (LAMA and LABA) are frequently used to treat the symptoms of COPD.

Brimica Genuair has been studied in 2 main studies involving over 3,400 patients with COPD, in which it was compared with aclidinium alone, formoterol alone and placebo (a dummy treatment). The main measure of effectiveness was based on changes in patients' forced expiratory volumes (FEV_1, the maximum volume of air a person can breathe out in one second) after six months.

Results showed that, after six months of treatment, the increase in FEV_1 (measured one hour after an inhalation) was 293 milliliters (ml) more with Brimica Genuair than with placebo and 118 ml more with Brimica Genuair than with aclidinium alone. However the improvement over formoterol alone was small and not considered clinically significant: FEV_1 measured in the morning before the inhalation was 68 ml

more with Brimica Genuair than with formoterol alone. Brimica Genuair was also shown to increase the percentage of patients who had an improvement in breathlessness compared with placebo.

Unknowns relating to treatment benefits

In the main studies, nearly all patients were adult Caucasians. No differences in efficacy and safety are expected in patients of different ethnic backgrounds but further studies are ongoing in Asian patients in Japan to provide information on the use of aclidinium/formoterol in this population.

Summary of safety concerns

Important identified risks

No important risks were identified from the clinical development of Brimica Genuair.

Important potential risks

Risk	**What is known**
Problems affecting the heart (cardiac events)	Aclidinium bromide is a LAMA and formoterol fumarate dihydrate is a LABA. Side effects, such as problems with the rhythm of the heart, heart attack and heart failure, have been reported to occur with other LAMAs and LABAs, and therefore are considered a potential risk with Brimica Genuair. In clinical studies, up to 7% of patients experienced any type of heart disorder, similarly to the rate seen with placebo, and fewer than 2% experienced a serious event. Most events were mild to moderately severe and most patients fully recovered or were recovering from the events. Brimica Genuair should be used with caution in patients who have had or have any heart disorders and may need to be stopped if any unfavourable effects, such as increased heart rate or increased blood pressure, occur.
Problems affecting the blood vessels in the brain (cerebrovascular events)	Side effects such as stroke have been reported to occur with other LAMAs and LABAs and are therefore considered potential risks with Brimica Genuair. In clinical studies, fewer than 1% of patients experienced any type of stroke-related event, similar to placebo.
Death (mortality)	Increased mortality has been observed in patients taking similar medicines. In studies with Brimica Genuair the number of deaths was similar in the groups taking Brimica Genuair and in the placebo group.
Side effects that mainly affect the urinary tract, eyes, heartbeat and blood sugar or potassium levels, which have been observed with LABA and LAMA medicines (class effects -	LABAs and LAMAs are known to affect multiple organ systems, not just the lungs. In clinical studies, fewer than 4% of patients experienced undesirable effects including high blood sugar, blurred vision, increased pressure in the eye (glaucoma), blood potassium decrease, fast heartbeat and urinary retention (inability to pass urine). Most events were mild to moderately severe and most patients fully

Risk	What is known
anticholinergic and beta2-agonist adverse effects)	recovered or were recovering from the events.
Alterations of the electrical activity of the heart (QTc prolongation)	No relevant alterations of the electrical activity of the heart on the electrocardiogram have been seen with aclidinium bromide (one of Brimica Genuair components), however in the published literature, it is described that formoterol (another Brimica Genuair component) could cause alterations on the recordings of the electrical activity of the heart. In the clinical studies, no important differences on the electrocardiogram were seen between patients treated with Brimica Genuair or placebo.
Temporary narrowing of the airways which occurs suddenly leading to difficulties in breathing or wheezing (paradoxical bronchospasm)	Worsening of COPD symptoms (paradoxical bronchospasm) were not observed in the clinical studies with Brimica Genuair. However, this effect has been observed with inhaled formulations of a number of other medicines for the treatment of COPD. The mechanisms that cause this are unknown. This condition is unpredictable in nature. If symptoms occur, treatment with Brimica Genuair should be stopped.
Allergic reactions (hypersensitivity)	In clinical studies, allergic reactions occurred in 0.5% of patients and were mostly mild or moderately severe and similar to placebo.
Unapproved use (off-label use) in asthmatic patients and events related to asthma	Brimica Genuair should not be used in patients with asthma. Clinical studies with Brimica Genuair have not been conducted in this population.
Unapproved use (off-label use) in children	Brimica Genuair should not be used in children or adolescents below 18 years of age. Clinical studies with Brimica Genuair have not been conducted in this population.
Medication errors	It is possible that doses will not be given properly when the device is used incorrectly. Doctors, nurses, and pharmacists should discuss with patients how to correctly use the inhaler.

Missing information

Risk	What is known
Use in patients with certain illnesses at the same time as COPD	Brimica Genuair has not been studied in patients suffering from the following conditions since the symptoms may get worse: • patients who have had heart problems recently (such as irregular heart beat [arrhythmias], heart attack [myocardial infarction], cardiac chest pain [angina]). Such patients were excluded from the clinical studies and these conditions may get worse; • patients with alterations of the electrical activity of the heart (QTc prolongation); • patients with an enlarged prostate (benign prostatic hyperplasia),

Risk	What is known
	problems passing urine (urinary retention), blockage in the bladder (bladder neck obstruction) or increased pressure in the eye (narrow angle glaucoma); • patients with thyroid gland problems (thyrotoxicosis) or a tumour in one of the adrenal glands (phaeochromocytoma).
Safety in patients with severe kidney or liver impairment	Since no dosage adjustments are needed for medicines containing either aclidinium or formoterol in patients with kidney or liver impairment, no dosage adjustment is required for Brimica Genuair. Nevertheless, clinical experience with Brimica Genuair in patients with severe liver or kidney impairment is limited.
Use together with other medicines containing similar active substances to aclidinium and formoterol (LAMAs or LABAs)	The use of Brimica Genuair together with other medicines containing similar active substances (LAMAs or LABAs) has not been studied and is therefore not recommended.
Use together with other medicines containing certain active substances to treat high blood pressure (non-selective beta blockers)	There is limited information on the concomitant use of Brimica Genuair with some medicines used for high blood pressure or for coronary (heart) artery diseases (non-selective beta blockers such as carvedilol or propranolol).
Use in patients with very severe COPD using Brimica Genuair in the long term	There is limited information in patients with very severe COPD using Brimica Genuair for more than 1 year.
Information on non-Caucasian patients	The number of non-Caucasian patients with COPD in the Brimica Genuair clinical development programme was low. No dosage adjustments are expected for Brimica Genuair on the basis of ethnicity. However, studies will take place in Asian patients.
Use in pregnancy and breastfeeding	There are no data available on the use of Brimica Genuair in pregnant or breastfeeding women. Brimica Genuair should only be used during pregnancy if the expected benefits outweigh the potential risks. Since it is unknown whether the active substances in Brimica Genuair and/or their metabolites pass into human breastmilk, the use of Brimica Genuair by breastfeeding women should only be considered if the expected benefit to the woman is greater than any possible risk to the infant.

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 Brimica Genuair can be found on Brimica Genuair'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**
M/34273/44: Post-authorisation safety study (PASS)	To evaluate the cardiovascular safety and all-cause mortality of aclidinium and other bronchodilators used in patients with COPD. When Brimica Genuair becomes available, new users will be included in the cohort for evaluation. A new additional endpoint of cardiac arrhythmias is planned to be evaluated for this cohort.	• Cardiac events (myocardial infarction, cardiac failure and cardiac arrhytmias) • Cerebrovascular events (stroke) • Mortality from all causes	Planned	Results for aclidinium monotherapy expected in first half 2017- first half 2020. Results for aclidinium/formoterol to be estimated depending on the market intake of the product after its launch (expected in 2015).
M/34273/43: Drug utilisation study (DUS 1 and DUS 2)	To describe the characteristics and patterns of use in new users of aclidinium (monotherapy or in combination) and new users of other	Safety of aclidinium in groups where information is missing. Potential off-label	Planned	Final report for DUS 2 expected in 2018-2019.

Study/activity (including study number)	Objectives	Safety concerns /efficacy issue addressed	Status	Planned date for submission of (interim and) final results
	selected COPD treatments. To evaluate the potential off-label use. To describe users of aclidinium in patient subgroups for which there is missing information. To establish a core cohort of new users of aclidinium.	use.		
KRP-AB1102F-D301 Phase 3	To verify the superiority of 12-week twice daily repeated treatment of Brimica Genuair over that of aclidinium in Japanese COPD patients and, in addition, to confirm the efficacy and safety of Brimica Genuair.	Efficacy and safety evaluation in non-Caucasian population.	Ongoing	Final report expected in April 2015.
KRP-AB1102F-D302 Phase 2	To assess the pharmacokinetics of aclidinium bromide and formoterol after repeated administration of Brimica Genuair (twice daily) for 5 days in Japanese male patients with COPD.	Efficacy and safety evaluation in non-Caucasian population.	Experimental phase completed	Final report expected in May 2014.
KRP-AB1102F-D303 Phase 3	To assess the safety and efficacy of long-term (52 weeks) administration of	Efficacy and safety evaluation in non-Caucasian population.	Ongoing	Final report expected in August 2015.

Study/activity (including study number)	Objectives	Safety concerns /efficacy issue addressed	Status	Planned date for submission of (interim and) final results
	Brimica Genuair in Japanese patients with COPD.			

Studies which are a condition of the marketing authorisation

The post-authorization safety study M/34273/44 is a condition of the marketing authorisation.

Summary of changes to the risk management plan over time

Not applicable.

This summary was last updated in 11-2014.