EMA/15860/2015

Summary of the risk management plan (RMP) for Mysimba (naltrexone / bupropion)

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

Overview of disease epidemiology

Mysimba is a medicine used together with diet and exercise to treat obesity, which is defined as a BMI (body-mass index, a measure of weight relative to height) of 30 or above; it can also be given to very overweight patients who have weight-related complications. Obesity can significantly reduce mental and physical health and quality of life and can be associated with wide-ranging complications including high blood pressure, high blood sugar levels (diabetes), coronary heart disease, stroke, some types of cancer and depression.

About 25% of the world population was estimated to be overweight in 2005. Within Europe, it is anticipated that up to 2 out of 3 people will be obese or overweight within the next 10 years. There is an association between obesity and older age and race. The most prominent reason for obesity is excess calorie intake combined with reduced physical activity.

Summary of treatment benefits

Mysimba contains the active substances naltrexone and bupropion, which act on the parts of the brain that control food intake and energy balance, as well as reducing the effect of the part of the brain that controls the pleasure associated with eating food. When given together, their actions reduce appetite and the amount that patients eat and increase energy expenditure, helping them to stick to a calorie-controlled diet and reduce their body weight.

The effects of Mysimba in reducing body weight have been shown in 4 main studies involving around 4,500 obese or overweight patients, in which Mysimba was compared with placebo (a dummy treatment). Patients in the studies were given the medicine as part of a weight loss programme involving counselling and advice on diet and exercise. The main measures of effectiveness were the percentage reduction in body weight over 28 or 56 weeks of treatment, and the proportion of patients who achieved at least a 5% weight reduction; the studies also looked at the number of patients who achieved at least a more stringent 10% reduction in weight, and the results were analysed using various methods to take account of the number of patients who did not complete the studies (around 50% over one year).

In three of the studies, the average weight loss in patients treated with Mysimba was around 3.7 to 5.7%, compared with 1.3 to 1.9% with placebo; the proportion of Mysimba-treated patients who achieved 5% weight loss ranged from 28 to 42% compared with 12 to 14% with placebo. About 13 to

22% of those taking Mysimba achieved at least a 10% reduction in weight, while 5 to 6% of placebo-treated patients did so.

In the other study, in which patient counselling was also more intensive, the overall weight loss was greater over the study period: 8.1% with Mysimba and 4.9% with placebo. Some 46% and 30% of patients given Mysimba achieved 5 and 10% weight reductions respectively, compared with 34% and 17% respectively with placebo.

The degree of improvement with Mysimba over placebo was similar using different methods of analysis, although the benefits were smallest with the most conservative methods that assumed patients who did not complete the study would not have seen any improvement. The treatment effect was more marked in patients who completed 56 weeks of treatment, or who had lost at least 5% of their original body weight by 4 months.

Unknowns relating to treatment benefits

Studies with Mysimba included a broadly representative selection of obese people; however, a majority of people were white, middle aged females. Experience in children and adolescents, pregnant or breastfeeding women, and patients with liver or kidney impairment is limited and it is therefore not known if the benefits and risks of the medicine are the same in these groups.

Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Fit (seizure)	Fits (seizures) may affect up to 1 in 1,000 people taking bupropion (one of the main ingredients in Mysimba). During studies with Mysimba, 2 out of 3,239 subjects experienced an isolated fit.	Can be largely prevented by following the warnings and precautions in the product information and not prescribing to patients at an increased risk of fits. A checklist is provided for the doctor to fill in, to ensure these warnings are borne in mind before prescribing Mysimba.
Interaction with other medicines	Certain other medicines may affect, or be affected, by Mysimba. These include certain medicines used to treat depression (MAOIs), strong painkillers (opioid–containing painkillers) or medicines which affect the enzymes in the liver that break down the active substances in Mysimba. If medicines are affected by Mysimba this means that either they will not be as effective or their effect may be increased, resulting in side effects. Similarly some medicines may cause Mysimba to be less effective or may	Can be largely prevented by doctors following the contraindications, warnings and precautions in the product information. A checklist is provided for the doctor to fill in, to ensure these are borne in mind before prescribing Mysimba.

Risk	What is known	Preventability
	increase the risk of side effects.	
Transient increases in blood pressure and heart rate	Obese patients are at increased risk of developing high blood pressure. Approximately 1 in 4 patients taking Mysimba had an increase in blood pressure during studies but in most subjects this effect did not last long or lead to any problems. Bupropion-containing medicines have been known to increase pulse rates and blood pressure in up to 1 in 100 patients.	Can be prevented by doctors following the indication (stopping rule) contraindications, warnings and precautions in the product information. These include monitoring of blood pressure and pulse before starting and during treatment, increasing the dose slowly at the start of treatment, and stopping treatment if there are clinically relevant increases in blood pressure or pulse. A checklist is provided for the doctor to fill in, to ensure these are borne in mind before prescribing Mysimba.
Allergy (hypersensitivity) including severe reactions like Stevens-Johnson Syndrome (a rare skin condition with severe blisters and bleeding in the lips, eyes, mouth, nose and genitals)	Overall, mild or moderate hypersensitivity reactions such as itchy rash (urticaria) are seen in up to 1 patient in 10 taking medicines containing bupropion, but severe hypersensitivity reactions have been very rarely reported (in up to 1 in 10,000 patients). Symptoms of severe hypersensitivity reactions include itching, a rash, swelling of eyelids, face, lips, tongue or throat, and/or chest pain, and difficulty in breathing requiring medical treatment.	It is not possible to predict who will experience a hypersensitivity reaction and so it cannot be prevented. However, if it occurs the seriousness can be reduced by patients stopping taking Mysimba immediately if they experience itching, rash, hives, chest pain, swelling of the face or mouth or shortness of breath.
Mental illness with strange or disturbing thoughts or moods (neuropsychiatric symptoms)	Abnormal dreams including nightmares, feeling anxious or lightheaded, tension, agitation and mood swings may affect up to 1 in 100 people taking Mysimba.Effects on mood and mental function have been reported when bupropion or naltrexone are taken alone.	When starting treatment, the dose should be increased slowly over 4 weeks. Mysimba should not be taken by people with a history of bipolar disorder and should be used cautiously in patients with a history of mania. When starting treatment or changing dose, patients and others close to them should watch out for changes in behaviour or mood and any worsening of suicidal behaviour or thoughts. A checklist is provided for the doctor to fill in, to ensure this risk is borne in mind before prescribing Mysimba.
Undesirable effects on the liver	Naltrexone (one of the active substances in Mysimba) may cause	Patients should not exceed the

Risk	What is known	Preventability
(hepatotoxicity)	damage to the liver when given in excessive doses (around 10 or more times the recommended daily dose in Mysimba). Such effects have not been observed in studies with Mysimba.	recommended dose.
Undesirable effects on the stomach	Feeling sick (nausea) and being sick (vomiting) are amongst the most frequent side effects for Mysimba (may affect more than 1 in 10 people). Symptoms typically resolve during the first 4 weeks of Mysimba treatment, generally without the need for other medicines to relieve them.	When starting treatment, the dose should be slowly increased over 4 weeks. Patients should not exceed the recommended dose.

Important potential risks

Risk	What is known
Suicidality in patients with depression	During initial studies with Mysimba, there were no suicides, suicide attempts, or suicidal behaviour observed. However, it is considered a potential risk because bupropion has antidepressant actions and depression may worsen in a minority of patients while on antidepressant treatment. Depression is associated with an increased risk of suicide-related events (such as suicidal thoughts, self-harm and attempted suicide) and an association between depression and obesity has been well-established previously. Analyses of clinical studies of antidepressants showed an increased risk of suicidal behaviour in people under the age of 25 years old.
Use of Mysimba outside the approved conditions (off-label use) and potential for abuse of Mysimba	Mysimba should only be prescribed to people who are obese or those who are overweight with diabetes, high cholesterol or controlled high blood pressure. There is a potential risk that Mysimba may be taken by other groups, since it is known that medicines to lose weight are sometimes wrongly taken by people (especially those with a history of anorexia or bulimia) who are of normal weight or below normal weight. There is also a risk that people who should not be prescribed Mysimba because they are at increased risk of side effects may be wrongly given the medicine.
Inflammation of the gallbladder (cholecystitis) associated with rapid weight loss	Gallstones, which are an important cause of gallbladder inflammation, are more likely in people who are overweight and obese (particularly in women and in those who are most obese) and are often triggered by rapid weight loss. Cholecystitis is therefore considered a potential risk of Mysimba treatment.
Birth defects (congenital malformations) in babies whose mothers take	In clinical studies with Mysimba, there were no cases of birth defects; however, the number of pregnancies was too small to draw definite conclusions. There are conflicting results from studies in women who were treated with

Risk	What is known
Mysimba	bupropion during the first 13 weeks of pregnancy. Some of these studies have reported an increased risk of certain heart defects in babies born to such women, whereas others have not. Because it is considered a potential risk, Mysimba should not be used during pregnancy or in women currently attempting to become pregnant.

Missing information

Risk	What is known
Limited information on use during pregnancy	Mysimba is not authorised for use in pregnancy or in women attempting to become pregnant, and it is not known if there is any risk of birth defects or whether Mysimba has any effect on growth and development in the womb. In clinical studies with Mysimba, there were no cases of birth defects; however, the number of pregnancies was too small to draw conclusions.
Limited information on use during breastfeeding	Naltrexone and bupropion have been detected in the milk of breastfeeding mothers taking these medicines. As there is limited information on the effects of these medicines in babies being breast-fed, a risk to the baby cannot be excluded. Mysimba should not be used during breastfeeding.
Limited information on effect on fertility	There are no data on the effects on fertility from the combined use of naltrexone and bupropion. No effect on fertility in animal studies has been observed with bupropion. In animal studies, naltrexone caused decreased pregnancy rates. The relevance of these observations to human fertility is not known.
Limited information on use in children and adolescents	As children and adolescents were not included in the studies leading to the licensing of Mysimba, its effects on this group of patients are unknown. Mysimba is not approved for use in children and adolescents under the age of 18 years.
Limited data on long-term use beyond 1 year	Data on long-term use of Mysimba beyond 1 year are limited. Potential side effects linked to such longer-term use are unknown. The need for continued treatment should be re-evaluated annually.
Limited information on use in patients with liver impairment	Studies in patients with liver disease have not been conducted and it is not known if the benefits and risks in these patients are the same as in other patients. The liver plays a role in breaking down bupropion into other substances in the body. Therefore Mysimba should not be taken by patients with severe liver disease and is not recommended in patients with mild or moderate liver disease.
Limited information on use in patients with severe or moderate kidney disease	There is limited information on the use of this medicine in patients with moderate or severe kidney damage. As the kidneys get rid of naltrexone and bupropion from the body, the risk of side effects may be greater in people whose kidneys do not work well and particularly in those with severe kidney damage. Therefore, Mysimba should not be taken by patients with severe or end-stage kidney disease and is not recommended in patients with moderate

Risk	What is known
	kidney disease.

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 Mysimba can be found on Mysimba's EPAR page.

This medicine has special conditions and restrictions for its safe and effective use (additional risk minimisation measures). Full details on these conditions and the key elements of any educational material can be found in Annex II of the product information which is published on Mysimba's EPAR page; how they are implemented in each country however will depend upon agreement between the marketing authorisation holder and the national authorities.

These additional risk minimisation measures are for the following risks:

Fits (Seizures)

Interaction with other medicines

Transient increases in blood pressure or heart rate

Mental illness with strange or disturbing thoughts or moods (neuropsychiatric symptoms)

Undesirable effects on the liver (hepatotoxicity)

Suicidality in patients with depression

Limited information on use in patients with severe or moderate kidney disease

Risk minimisation measure: Guide for doctors
Objective and rationale: • To remind doctors that patients with fits or a history of fits should not be prescribed Mysimba • To remind doctors that patients with a known brain tumour should not be prescribed Mysimba • To educate and remind doctors about additional risk factors for fits • To remind and inform doctors about medicines which should not be prescribed at the same time as Mysimba • To remind doctors about other medicines which may make fits more likely • To remind doctors that patients with uncontrolled high blood pressure shouldn't be prescribed Mysimba • To remind doctors that patients with bipolar disorder (a mental illness causing alternating periods of high mood and depression) should not be prescribed Mysimba • To inform and educate doctors about the identified risk of mental illness associated with the use of

Risk minimisation measure: Guide for doctors
Mysimba • To educate and remind doctors that patients who have depression or a history of mania should only be prescribed Mysimba if the expected benefits outweigh the possible risks about additional risk factors for mental illness • To remind doctors that patients with depression or with a history of attempted suicide should only be prescribed Mysimba if the expected benefits outweigh the possible risks • To remind doctors that young people are at particular risk of suicidal thoughts • To remind doctors that patients with severe liver disorders should not be prescribed Mysimba • To remind doctors that patients with end-stage kidney disease or severe kidney disorders should not be prescribed Mysimba • To remind doctors that patients with moderate kidney disorders should only be prescribed Mysimba if the expected benefits outweigh the possible risks • To remind doctors to test kidney function for patients at greater risk for poor kidney function, in particular, individuals with diabetes or elderly individuals, prior to starting Mysimba • To provide an aide memoire to ensure appropriate patient selection • To reinforce what Mysimba is used for
Description: A guide is provided to doctors who are expected to prescribe Mysimba, including a checklist of the considerations to be borne in mind before Mysimba is prescribed to each patient, and a reminder of the need to stop treatment if there are concerns about safety or if patients do not lose at least 5% of their original body weight after 16 weeks.

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**
NB-CVOT study 1 - A multicenter, randomized, double-blind, placebo-controlled study assessing the occurrence of major adverse cardiovascular events (MACE) in overweight and obese subjects with cardiovascular risk	Determine the effects of Mysimba relative to placebo (a dummy treatment) on major adverse cardiovascular events (MACE; serious effects on the heart and circulation) including cardiovascular death, non-fatal	Major cardiovascular events; Serious events; Events leading to stopping treatment; Exposure in patients with co-morbidities (e.g. depression) and taking other medications of interest (e.g. anti-depressants)	Started	First interim report May 2014; Second interim report (50% of events) targeted by mid 2015; Final study report planned for 4th quarter 2017

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
factors receiving naltrexone SR/bupropion SR	heart attack (myocardial infarction), and non-fatal stroke in overweight and obese subjects who are at a high risk of having these events because they have diabetes and/or other cardiovascular risk factors.			
NB-CVOT study 2 – A multicenter, randomized, double-blind, placebo-controlled, phase 4 study to assess the effect of naltrexone extended release (ER) /bupropion ER on the occurrence of major adverse cardiovascular events (MACE) in overweight and obese subjects with cardiovascular disease	Determine the effects of Mysimba relative to placebo on major adverse cardiovascular events (MACE) in overweight and obese subjects who are at a higher risk of having events because they have a history of cardiovascular disease with or without diabetes	Major cardiovascular events Serious events; Events leading to stopping treatment; Relevant non-cardiovascular events (e.g. mental illness events, liver toxicity, transient high blood pressure) Exposure in patients with co-morbidities (e.g. depression) and on concomitant medications of interest (e.g. anti-depressants)	Planned	Protocol submission: 31 March 2015 Study Enrolment: 2nd half of 2015 Final study report: 1st quarter of 2022
Naltrexone/ Bupropion (NB) drug utilisation study (DUS): retrospective chart review & nested NB prescribing physician cross sectional survey	To evaluate how Mysimba is used in real world medical practice:		Planned	Interim report: 24 months after Mysimba launch Final study report: 42 months after Mysimba launch
	To characterise	• Age, sex and other demographics;		

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
	users of Mysimba	• Patient comorbidity; • Patient subgroups for which there is missing information i.e.: • Women pregnant, breastfeeding, or seeking pregnancy; • Paediatric patients; • Patients with liver impairment; • Patients with severe kidney impairment; • Potential for use outside the indication, abuse potential, and use in contraindicated conditions		
	To evaluate the pattern of use of Mysimba	• Dose and duration of treatment, including identification of long-term and chronic use, and changes in prescribing after week 16 of treatment; • Use of concurrent/ concomitant medications • Specialty of the prescribing physician		
	To assess the incidence of important identified and potential safety risks	• Fits (seizures) • Transient increase of blood pressure and heart rate • Hypersensitivity reactions • Mental health illness symptoms • Liver toxicity • Gastrointestinal disorders • Suicide and suicidal behaviour		

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
		• Cholecystitis • Congenital malformations		
	To evaluate the effectiveness of the checklist for doctors as a tool for risk minimisation	• To evaluate whether physicians prescribing Mysimba have received, understood and complied with the checklist as part of physician packet provided prior to supply of the medicine		
Naltrexone/ Bupropion observational database study	To assess the incidence of important identified and potential safety risks	• Fits (seizures) • Transient increase of blood pressure and heart rate • Hypersensitivity • Mental health illness symptoms • Liver toxicity • Gastrointestinal disorders • Suicide and suicidal behaviour • Cholecystitis • Congenital malformations	Planned	Interim report: After 1500 patients with Mysimba is reached Second Interim report: 3 years after Mysimba launch Final study report: 3 months after the 5 year analysis has been completed in the last country/ database
	To characterise users of Mysimba	• Use in subgroups for which there is missing information e.g. pregnancy, breastfeeding, paediatrics patients • Use in contra-indicated populations		
	To evaluate the pattern of use of Mysimba	• Use of concurrent/ concomitant medications potentially interacting		

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
		with Mysimba • Specialty of the prescribing physician		
Renal impairment study: effect of renal impairment on the pharmacokinetics of naltrexone PR/ bupropion PR tablets	Primary To assess the pharmacokinetics (distribution in the body) following multiple dosing with Mysimba in subjects with mild, moderate or severe kidney disease compared with subjects with normal kidney function. Secondary To assess the safety and tolerability of Mysimba in subjects with kidney disease.	Missing safety information on use in patients with severe or moderate kidney disease	Planned	Final Report Submission: August 2017
Hepatic impairment study: effect of hepatic impairment on the pharmacokinetics of naltrexone PR /bupropion PR tablets	Primary To assess the pharmacokinetics following multiple dosing with Mysimba in subjects with mild, moderate or severe liver disease compared with subjects with normal liver function Secondary To assess the safety and tolerability of	Missing safety information on use in patients with liver disease	Planned	Final Report Submission: August 2018

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
	Mysimba in subjects with liver disease			
A Phase 1, open-label study to assess the effects of repeated dosing with naltrexone extended release (ER)/Bupropion ER combination trilayer tablets on the single-dose pharmacokinetics (PK) of metformin in healthy adult subjects	Primary To assess the effect of Mysimba on the single-dose pharmacokinetics of metformin in healthy adult subjects. Secondary To assess the safety and tolerability of the treatments received throughout the duration of the study.	Missing information on interaction with metformin	Planned	Final Report Submission: January 2017
Thorough QT study	To confirm there is no effect of Mysimba on the heart's electrical cycle (QT interval).	Missing information of effect of Mysimba on the heart's electrical cycle (QT interval).	Planned	Final Report Submission: March 2017

Studies which are a condition of the marketing authorisation

NB-CVOT study 2 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 03-2015.