1.10.2015

VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Bupropion for depression

The number of people with major depressive disorders varies throughout Europe. Research estimates that 4.4% of people have major depressive disorder (MDD) when conducted during 1990, 2005 and 2010. In a study conducted in patients with MDD the majority were women (70.8%). Some risk factors for MDD include previous history, gender, diet, obesity, and occupational status. Treatment for MDD includes medicines, psychotherapy, and electroconvulsive therapy. Depressive disorders may contribute to suicide, heart disease and dementia in the elderly. One study found that hypertension, asthma, type 2 diabetes mellitus, anxiety disorder, alcohol dependence, and nicotine dependence were the most common conditions associated with MDD. In depressed patients that have died the most common contributing conditions to death were chronic obstructive pulmonary disease, type 2 diabetes mellitus, atrial fibrillation, pneumonia and cataract.

Bupropion for smoking cessation

Across Europe an average of 23% of adults (aged ≥15) smoked daily in 2010. In Europe more males tend to smoke than females. Nicotine dependent smoking may be associated with high caffeine use, regular use of drugs, suicide attempts, and with primary or lower education. One study found that girls that were prenatally exposed to maternal tobacco use had higher odds of experiencing craving for tobacco. No significant association was found for boys. Counseling and/or medication may be used to help stop smoking. Medications that are available in Europe include Nicotine Replacement Therapy (NRT), bupropion and varenicline. Tobacco was estimated to cause 5.1 million deaths globally in 2004 which equates to almost 1 in 8 deaths in adults aged older than 30. Some of the most illnesses associated with smoking are chronic bronchitis, emphysema and heart attack.

VI.2.2 Summary of treatment benefits

Bupropion for depression

- In the first of two identical studies of comprising 576 individuals bupropion XL (150 to 300 mg/day) was statistically significantly superior to placebo on the primary parameter, change from baseline on a scale used to measure depression [Montgomery-Asberg Depression Rating Scale (MADRS)]. The effectiveness of bupropion XL in this study was similar to that of the comparator, venlafaxine.

- In a second study of 591 individuals, bupropion XL did not differ significantly from placebo for the primary parameter, change from baseline in MADRS total score, although statistically significant effects were seen for venlafaxine.

- In study of 274 adult patients with MDD and reduced levels of pleasure, interest and energy bupropion XL showed statistically significantly greater improvement over placebo for the primary parameter, change from baseline on a scale used to measure depression [Inventory of Depressive Symptomatology (IDS)]. Statistical significance was also shown for a number of secondary measures.

- Bupropion SR has also demonstrated comparable effectiveness to other antidepressants (sertraline, fluoxetine, and paroxetine) in controlled outpatient trials of up to 16 weeks duration.

Bupropion for smoking cessation

Studies have demonstrated the effectiveness of bupropion in smokers who are motivated to quit. The primary effectiveness measure in each of these studies was stopping smoking for a four-week period. This measure is the generally accepted international regulatory criterion for approval of an aid to smoking cessation.

- Bupropion was most effective at 300mg in one study

- A second study demonstrated that bupropion SR was more effective than a nicotine transdermal system (NTS) and that a combination of bupropion SR and NTS led to greater effectiveness than either treatment alone.

- Patients randomised to Zyban in one study for up to 52 weeks had a longer median time to relapse compared with patients who took placebo.

VI.2.3 Unknowns relating to treatment benefits

Although certain groups of patients were excluded from clinical studies with bupropion the extensive market exposure means that such patients will have been exposed in the 25 years that bupropion has been available. Large differences in bupropion effectiveness are not expected within the depressed or smoking populations.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Fits/Seizures	Fits/seizures are rare (less than 1 in 1000 treated patients) and the risk is related to dose. Although the seizures will cease after stopping treatment with this medicine, having had a seizure may affect the patient's driving licence and/or ability to operate machinery. The patient may also injure himself during the seizure.	It is important to follow the instructions in the package leaflet provided with this medicine. This includes taking only the amount prescribed (not more), not splitting the tablet. There is also advice not to take this medicine if the patient has other conditions (e.g. previous seizures). It is also important to inform the doctor what other medicines the patient is taking as combination of some medicines may increase the risk of convulsions.
Allergic reactions	Some persons are allergic to this medicine. The allergy may include red skin or rash (like nettle rash), blisters or itchy lumps (hives) on the skin. More severe allergies include unusual wheezing and difficulty in breathing, collapse or blackout	The types of allergic reaction are described in the package leaflet. If an allergic reaction is suspected, the patient should not take any more of this medicine and consult a doctor urgently.
Increase in blood pressure	This medicine can increase the blood pressure and the risk is greater if the patient is also using nicotine replacement patches in order to stop smoking.	The doctor may check the patient's blood pressure before starting treatment with this medicine and at intervals during treatment.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Reduced numbers of blood cells: red blood cells (anaemia), white blood cells (leucopenia) and platelets (thrombocytopenia)	There are very few reports of a reduction in blood cells while taking this medicine Whether all of those cases are due to this medicine is currently not known.
Acute angle closure glaucoma/Increased pressure in the eyeball	Some types of antidepressant medicine have been known to increase the pressure in the eyeball (a condition called glaucoma, particularly the type known as "acute angle closure glaucoma"). Urgent medical treatment of acute angle closure glaucoma is necessary to prevent permanent damage to the eyesight. However whether this medicine causes acute angle closure glaucoma is currently not known.
Irregular heartbeats	Some medicines can increase the risk of irregular heartbeats and in rare circumstances the irregularity can lead to death. There are reports of the more dangerous types of irregular heartbeats when an overdose of this medicine has been taken. These dangerous irregularities are currently not known to happen when the correct dose of this medicine is used.
Deaths	There are reports of deaths after overdoses of this medicine, in particular when taken with overdoses of other medicines and/or illegal drugs.
Suicide attempts and thoughts of suicide	This medicine is used as an antidepressant and also used as an aid to stop smoking. Severe depression can result in thoughts of suicide and attempts to kill oneself. Most antidepressants take a while to be effective and before the patient recovers, carers are advised to watch the behaviour of the patient being treated, particularly at early stages of treatment and when the dose of antidepressant medicine is changed. It is also known that a smoker who is reducing the amount smoked or stopping smoking can feel suicidal. This is an effect of nicotine withdrawal and it is difficult to distinguish nicotine withdrawal from a potential side effect of this medicine.
Psychological effects and effects on the nerves when this medicine is used to stop smoking	When smokers are attempting to stop smoking, there are psychological and nerve effects from reducing the amount of nicotine in the body. These include feeling depressed or suicidal, being agitated, feeling hostile and other abnormal feelings. It is difficult to distinguish nicotine withdrawal from

Risk	What is known (Including reason why it is considered a potential risk)
	potential side effects of this medicine.
Heart and blood vessel malformations in babies when mother has taken this medicine during pregnancy	There are reports of heart and blood vessel malformations in babies born to mothers who have taken this medicine during pregnancy. It has not been shown whether the malformation is due to this medicine for the following reasons: • These malformations are also seen when the mothers have not been treated with this medicine. • When a medicine causes a malformation, there is usually a pattern. There is no pattern for this medicine; the reports are a mixture of different types of malformations. The lack of a similar pattern makes it difficult to assess whether this medicine is at fault.
Errors in taking the medicine	The package leaflet provided to patients who have been prescribed this medicine contains information to limit the risk of side effects including the more severe ones like convulsions. However there have been instances where the instructions have not been followed. For example, patients are advised to swallow the tablet whole and not cut or chew it. Breaking up the tablet releases the active ingredients more quickly and increases a risk of convulsion.
Risk of cancer	Up till now, there is no increase in the risk of cancer when this medicine is taken. However health authorities and medicine manufacturers regularly review all medicines to see if there is an increased risk of cancer.
Low levels of a certain salt (sodium) in the body	Some types of medicine (including some antidepressants) affect specific salt (sodium) levels in the body. At present, there is no evidence that this medicine has that effect but reports of low sodium levels are being monitored during the routine review of the safety of medicines.

Missing information

Not applicable.

VI.2.5 Summary of additional risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

The Summary of Product Characteristics and the Package leaflet for bupropion can be found in the bupropion 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 in bupropion EPAR page; how they are implemented in each country however will depend upon agreement between the manufacturer and the national authorities.

These additional risk minimisation measures are for the following risks:

Medication Errors

Risk minimisation measure(s)
Objective and rationale
Medication errors relating to confusion between different bupropion formulations. Healthcare professional education on the different formulations of available bupropion to minimise the risk of medication errors. Objective and rationale: Patients and HCPs to understand the risk of confusion between different formulations of bupropion and the appropriate management of this risk to minimise its occurrence. Proposed action: HCP education materials to be provided to prescribing physicians and pharmacists including advice on: – Bupropion XR tablet (WELLBUTRIN XR/ELONTRIL) is a once daily medication for the treatment of depression. It should be distinguished from bupropion sustained-release tablets which are also available Europe as: – WELLBUTRIN SR which is a twice daily medication for the treatment of depression. – ZYBAN which a twice daily medication used as an aid to smoking cessation. – WELLBUTRIN XR/ELONTRIL, WELLBUTRIN SR and ZYBAN all contain the same

Risk minimisation measure(s)
active ingredient (bupropion hydrochloride) and should not be used together – Bupropion XR tablet should be swallowed whole and not be crushed or chewed – The maximum daily dose of bupropion extended-release tablet should not be exceeded

VI.2.6 Planned post authorisation development plan

List of studies in post authorisation development plan

Bupropion is approved for depression and smoking cessation in the EU. There are no plans for post-authorisation effectiveness studies or development of bupropion for treatments of othermedical conditions. Studies to investigate potential safety issues are summarized in the table below.

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
Can social listening data be used to provide meaningful insights into abuse or inappropriate use of bupropion? (A feasibility analysis) Social media listening study Non-interventional Category 3	To determine if social media can identify cases of potential abuse or inappropriate use of bupropion which can complement existing sources of information on abuse potential To explore the utility of various internet sites and forums or populations to identify cases of interest To describe and characterize the posts of interest (POI) identified during this feasibility analysis	Bupropion abuse and misuse potential	Protocol uploaded on EU-PAS register; data collection started 24 Jan 2015 Ongoing	Completion of final study report Q1 2016
A Phase 4, Randomized, Double-blind, Active And Placebo - Controlled, Multicenter Study Evaluating The Neuropsychiatric Safety And Efficacy Of 12	To characterize the neuropsychiatric safety profiles of varenicline and bupropion by estimating the differences from placebo in the incidence of the primary neuropsychiatric	Neuropsychiatric adverse events	Ongoing	Planned final report submission in 2017

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
Weeks Varenicline Tartrate 1mg Bid And Bupropion Hydrochloride 150mg Bid For Smoking Cessation In Subjects With And Without A History Of Psychiatric Disorders Interventional clinical study Category 3	AE endpoint for subjects: with a diagnosis of psychiatric disorder; and without a diagnosis of psychiatric disorder. To characterize the differences in the neuropsychiatric safety profiles of varenicline and bupropion as compared with placebo between these sub-populations (cohorts).			
PRJ2215: Assessment of Bupropion Misuse and Abuse 2004-2011 (Epidemiology study) Category 3	To investigate the degree of misuse and abuse of bupropion, including non-oral routes of administration, in the United States. Surveillance data from the Drug Abuse Warning Network (DAWN) was used to examine the study period 2004-2011.	Bupropion abuse and misuse	Completed	June 2014
ZYB117211: Incidence of Cardiovascular Related Adverse Events in Controlled Clinical Trials of Bupropion for the Treatment of	The objective of this investigation was to compare the incidence of adverse cardiovascular events in Zyban-treated groups versus control	Cardiovascular events	Completed	June 2014

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
Smoking Cessation (Meta-analysis study) Category 3	groups in previously completed randomized clinical trials of smoking cessation treatment.			
Study WEUKSTV1113: Risk of Cancer in Patients Exposed to Bupropion Epidemiology study Category 2	To compare the incidence of cancer in patients exposed to bupropion with the incidence in patients exposed to other antidepressants	Carcinogenicity	Completed	March 2010
i3 Study: Bupropion in Pregnancy and the Occurrence of Cardiovascular and Major Congenital Malformation Epidemiology study Category 3	To estimate the prevalence of all congenital malformations, and cardiovascular malformations in particular, among infants born to women exposed to bupropion in the first trimester of pregnancy.	Congenital cardiovascular malformations	Completed	2006
Re-analysis of the i3 study: Bupropion in Pregnancy and the Occurrence of Cardiovascular and Major Congenital Malformation Epidemiology study	Classify the bupropion cohort from the original study according to infants born to women who only received bupropion during the first trimester (i.e., bupropion first trimester monotherapy), and according to	Congenital cardiovascular malformations	Completed	2010

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
Category 3	infants born to women with any dispensing of bupropion alone or with another antidepressant during the first trimester (i.e., bupropion first trimester mono- or polytherapy). Maintain the 2 comparator cohorts from the original study (maternal bupropion use outside first trimester and other antidepressant use during first trimester) but classify them into monotherapy and mono- or polytherapy subgroups Provide lists of specific cardiovascular defects and defect groupings among the cohorts above with input from a pediatric cardiology expert. Calculate the prevalence for specific cardiovascular defects/groups among the cohorts above.			

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
	Calculate adjusted ORs for specific cardiovascular defects/groups and stratify the cohorts according to maternal dispensing of medications thought to be teratogenic, where numbers permit.			
First Trimester Exposure to Bupropion in Relation to the Risk of Cardiac Defects Epidemiology study Category 3	To investigate whether bupropion is associated with an increased risk of certain cardiac defects, specifically VSD, left outflow tract heart defects considered as a group, coarctation of the aorta, and hypoplastic left heart syndrome	Congenital cardiovascular malformations	Completed	Nov 2012

Studies which are a condition of the marketing authorisation

Conduct of study WEUKSTV1113 (Risk of Cancer in Patients Exposed to Bupropion) was a condition of marketing authorization.