SUMMARY OF ACTIVITIES IN THE RISK MANAGEMENT PLAN BY PRODUCT (VOXRA)

I Elements for summary tables in the EPAR

Summary of safety concerns	
Important identified risks	Seizures Increased blood pressure Inappropriate route of administration
Important potential risks	Abuse and misuse Pancytopenia Acute angle-closure glaucoma Increased intraocular pressure Arrhythmias and Conduction Disorders (potential at therapeutic doses) Fatalities Suicidality (Suicidal behaviour and thoughts) Pregnancies – congenital cardiovascular malformations
Missing information	None

II Table of on-going and planned additional PhV studies/activities in the Pharmacovigilance Plan

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)**
Subject Understanding of the Risks Associated with ZYBAN®, WELLBUTRIN®, WELLBUTRIN SR®, and WELLBUTRIN XL® Wave 3: 7‑Year Patient Knowledge, Attitudes, and Behavior Survey	To evaluate the practical aspects of use of the medication guide To assess patients' understanding of the serious risks associated with the use of bupropion for smoking cessation.	This is a survey study to assess subjects' knowledge of the serious risks of bupropion as described in the Medication Guides in the US.	Survey in progress	Final study report due to FDA Q1 2017

III Summary of post authorisation efficacy development plan

Not applicable

IV Summary table of Risk Minimisation Measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Seizure	Seizure is well documented in the bupropion CSI. SmPC section 4.3 contains information relating to contraindication of bupropion use in patients with seizure disorder and a history of seizures. SmPC section 4.4 contains clear warnings regarding the most important predisposing factors for seizure SmPC section 4.5 states that there is a risk of a potential interaction with medicinal products known to lower seizure threshold. SmPC section 4.8 lists seizure.	No additional risk minimization measures.
Increased blood pressure	SmPC section 4.8 states increased in blood pressure (sometimes severe) as an undesirable effect. SmPC section 4.4 states that hypertension can occur with and without use of a NTS. A higher rate of treatment-emergent hypertension was noted in the combination therapy group. Should NTS be used in combination with bupropion, weekly monitoring of blood pressure is recommended.	No additional risk minimization measures
Inappropropriate routes of administration	SmPC section 4.4 states WELLBUTRIN XR/Zyban is intended for oral use only. The inhalation of crushed tablets or injection of dissolved bupropion has been reported, and may lead to a rapid release, faster absorption and a potential overdose.	No additional risk minmisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Seizures and/or cases of death have been reported when bupropion has been administered intra-nasally or by parenteral injection.	
Abuse and misue potential	SmPC section 4.4 states the potential for drug abuse based on animal data but low abuse potential is considered in humans due to extensive clinical experience. SmPC section 4.4 states WELLBUTRIN XR/Zyban is intended for oral use only. The inhalation of crushed tablets or injection of dissolved bupropion has been reported, and may lead to a rapid release, faster absorption and a potential overdose. Seizures and/or cases of death have been reported when bupropion has been administered intra-nasally or by parenteral injection.	No additional risk minmisation measures
Pancytopenia	SmPC section 4.8 was updated to include anaemia, leukopenia and thrombocytopenia as undesirable effects under the blood and lymphatic system disorders SOC. No routine risk minimisation proposed for pancytopenia due lack of causal association up to date.	No additional risk minimization measures
Acute angle closure glaucoma	Section 5.7 (Warnings and Precautions) of the US Prescriber Information was updated to state that the pupillary dilation that occurs following use of many antidepressant drugs including bupropion may trigger an angle-closure attack in a patient with anatomically narrow angles who does not have a patent iridectomy.	No additional risk minimization measures.
Increased intraocular pressure	None proposed	No additional risk minimization measures
Arrhythmias and conduction disorders	SmPC Section 4.9 states ECG changes such as conduction disturbances	No additional risk minimization

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	(including QRS prolongation), arrhythmias and tachycardia may occur in overdose. QTc prolongation has also been reported but was generally seen in conjunction with QRS prolongation and increased heart rate.	measures
Fatalities	None proposed	No additional risk minimization measures
Suicidality	The Warnings and Precautions section of the bupropion CSI and SmPC section 4.4 for the smoking cessation indication notes that depression, rarely including suicidal ideation, has been reported in patients undergoing a smoking cessation attempt. Clinicians should be aware of the possible emergence of significant depressive symptomatology in patients undergoing a smoking cessation attempt. For the depression indication, warnings regarding clinical worsening and suicide risk associated with psychiatric disorders are included in the CSI and section 4.4 of the bupropion XL SmPC. SmPC section 4.8 lists suicidal ideation and suicidal behaviour (frequency not known) The bupropion US prescriber information includes a class 'black box' warning on suicidality with antidepressants.	No additional risk minimization measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Pregnancy – congenital cardiovascular malformations	SmPC section 4.6 states that some epidemiological studies of pregnancy outcomes following maternal exposure to bupropion in the first trimester have reported an association with increased risk of certain congenital cardiovascular malformations specifically ventricular septal defects and left outflow tract heart defects. These findings are not consistent across studies. SmPC section 4.6 for Wellbutrin XL contains a statement that it should not be used during pregnancy unless the clinical condition of the woman requires treatment with bupropion and alternative treatments are not an option. Section SmPC section 4.6 for Zyban states that Zyban should not be used in pregnancy. Pregnant women should be encouraged to quit smoking without the use of pharmacotherapy.	No additional risk minimization measures

V Elements for a Public Summary

V.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.

V.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.

V.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 30 years that bupropion has been available. Large differences in bupropion effectiveness are not expected within the depressed or smoking populations.

V.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.

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.

Risk	What is known (Including reason why it is considered a potential risk)
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.

Missing information

Not applicable.

V.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.

V.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	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	Bupropion abuse and misuse potential	Completed	Study report will be submitted with this RMP.

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)
Non-interventional Category 3	cases of interest To describe and characterize the posts of interest (POI) identified during this feasibility analysis			
A Phase 4, Randomized, Double-blind, Active And Placebo - Controlled, Multicenter Study Evaluating The Neuropsychiatric Safety And Efficacy Of 12 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	To characterize the neuropsychiatric safety profiles of varenicline and bupropion by estimating the differences from placebo in the incidence of the primary neuropsychiatric 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).	Neuropsychiatric adverse events	Completed	
PRJ2215: Assessment of Bupropion Misuse and Abuse 2004-2011 (Epidemiology study)	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	Bupropion abuse and misuse	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)
Category 3	(DAWN) was used to examine the study period 2004-2011.			
ZYB117211: Incidence of Cardiovascular Related Adverse Events in Controlled Clinical Trials of Bupropion for the Treatment of Smoking Cessation (Meta-analysis study) Category 3	The objective of this investigation was to compare the incidence of adverse cardiovascular events in Zyban-treated groups versus control groups in previously completed randomized clinical trials of smoking cessation treatment.	Cardiovascular events	Completed	June 2014
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

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)
Re-analysis of the i3 study: Bupropion in Pregnancy and the Occurrence of Cardiovascular and Major Congenital Malformation Epidemiology study Category 3	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 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	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)
	cardiovascular defects/groups among the cohorts above. 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.

V.7 Summary of changes to the Risk Management Plan over time

Major Changes to the Risk Management Plan Over Time

Version	Date	Safety Concerns	Comment
Version 1	February 2006	N/A	No changes made
Version 2	22 August 2007	Addition of carcinogenicity as an important potential risk	

Version	Date	Safety Concerns	Comment
Version 2	22 August 2007	Addition of increased intraocular pressure as an important identified risk	
Version 3	15 February 2008	Update to important potential risk of increased intraocular pressure	Results from a double-blind, randomised placebo controlled trial (WXL108709) in healthy volunteers; WELLBUTRIN XL did not show significant increases in IOP relative to placebo. No action required.
Version 4	13 August 2008	Update to important potential risk of suicidality	Results of a suicidality analysis are considered consistent with the current benefit-risk profile of bupropion for all its indications. No action required.
Version 4	13 August 2008	Termination of the Bupropion Pregnancy Registry:	Monitoring will continue via spontaneous reports and if warranted, established healthcare databases. No action required.
Version 5	26 April 2010	Update to important potential risk of carcinogenicity	Results obtained demonstrate that bupropion is not associated with an increased risk for all cancers combined (prostate, breast, lung, colon/rectum, urinary bladder, and uterus), compared with all antidepressants or with each of the three classes (TCAs, SSRIs, and others). However, an association was observed with three individual smoking-related cancers; lung and bladder when bupropion was compared to all antidepressants and colorectal cancer when bupropion was compared to other antidepressants (i.e. non-TCA, non-SSRI) alone. However, this association is thought to be due to residual confounding. No implications, no action required.
Version 5.1	14 June 2010	Update to important potential risk of carcinogenicity	Following submission of the results of the carcinogenicity study (RMP v5) to regulatory authorities, additional analyses are being performed as requested by EU authorities. Implications unknown.
Version 6	18 February	Update to important potential	Additional analyses have been

Version	Date	Safety Concerns	Comment
	2011	risk of carcinogenicity	conducted which confirmed that observed associations for lung, bladder and colorectal cancer are due to residual confounding by smoking. No implications, no action required.
Version 6	18 February 2011	Update to important potential risk of pregnancies: specific cardiovascular malformations study (Left Ventricular Outflow Tract Defects)	Following a publication by *Alwan et al*. 2010 of an increased risk of left-sided cardiac outflow tract defects with bupropion using data from the National Birth Defects Prevention Study (NBDPS), GSK commissioned re-analysis of archived data from their retrospective cohort study (conducted by Ingenix, now i3); results were inconclusive. A study using the Slone Epidemiology Center Birth Defects Study is being planned to investigate ventricular outflow tract defects further. No implications at this time.
Version 7	02 November 2012	Update to important potential risk of pregnancies: specific cardiovascular malformations study (Left Ventricular Outflow Tract Defects)	A Dear Health Care Provider Letter was submitted to the RMS for approval prior to distribution in the EU. The pregnancy section of the global datasheet was updated to include findings from the pregnancy studies and to update the benefit-risk statement. Minor updates to the non-clinical information were also included for clarity.
Version 8	19 February 2015	EU-RMP converted into new format	
Version 8	19 February 2015	Addition of inappropriate routes of administration as an important identified risk	Addition based on spontaneous reports of snorting and parenteral injection The global datasheet was updated to warn prescribers of the serious risks of inappropriate routes of administration
Version 8	19 February 2015	Addition of bupropion abuse and misuse as an important potential risk	Addition based on a request from RMS following review of addition of wording in the SmPC referring to inappropriate routes of administration.

Version	Date	Safety Concerns	Comment
Version 8	19 February 2015	Addition of acute angle closure glaucoma as an important potential risk	Addition based on antidepressant class labelling in US
Version 8	19 February 2015	Addition of pancytopenia and haematopoietic cytopenias as important potential risks	Addition based on cumulative review requested by PRAC. SmPC updated with anaemia, thrombocytopenia and leukopenia.
Version 9	December 2016	Removal of Hypersensitivity reactions from important identified risk	SmPC contains appropropriate information and low rate of reporting for over 10 years.
Version 9	December 2016	Removal of medication errors from important potential risks.	Monioring of medication errors since launch in Europe has shown very few reports.
Version 9	December 2016	Removal of carcinogenicity from important potential risk	Study WEUKSTV1113: (Risk of Cancer in Patients Exposed to Bupropion Epidemiology study) showed no risk associated with bupropion
Version 9	December 2016	Removal of hyponatraemia from important identified risk	SmPC contains appropropriate information
Version 9	December 2016	Removal of individual haematopoietic cytopenias from important identified risk	SmPC contains appropropriate information on anaemia, leukopenia and thrombocytopenia