PUBLIC ASSESSMENT REPORT
of the Medicines Evaluation Board
in the Netherlands

Wellbutrin XR, modified release tablets 150 mg and 300 mg
GlaxoSmithKline

bupropion hydrochloride

This assessment report is published by the MEB pursuant to Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.
To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has commented on this report for the absence of any confidential information.

EU-procedure number: NL/H/785/01-02/DC
Registration number in the Netherlands: RVG 33668-33669

8 June 2007

Pharmacotherapeutic group:	antidepressant
ATC code:	not available, for bupropion there is only the ATC code for indication smoking cessation which is not applicable for this product
Route of administration:	oral
Therapeutic indication:	Treatment of major depressive episodes
Prescription status:	prescription only
Date of end procedure:	22 December 2006 (day 164 of procedure)
Application type/legal basis:	Directive 2001/83/EC, Article 8(3), known active substance

For product information for healthcare professionals and users, including information on pack sizes and presentations see modules 2, 3 and 4.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Wellbutrin XR, 150 mg and 300 mg modified release tablets, from GlaxoSmithKline. The first date of authorisation was on 10 January 2007 in The Netherlands. The product is indicated for the treatment of major depressive episodes.

A comprehensive description of the indications and posology is given in the SPC (see Module 3).

The marketing authorisation has been granted pursuant to Article 8(3) – known active substance - of Directive 2001/83/EC.

Before submitting the application the applicant has requested scientific advice several times. Issues raised during these meetings were long term study protocol design, need for additional European studies with XR formulation and choice of active comparator and need for study in the elderly.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice

The RMS has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for these product types at all sites responsible for the manufacture and assembly of this product.
For the manufacturing site within the Community, the RMS has accepted a copy of the current manufacturer authorisation and a GMP statement issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For the manufacturing site outside the Community (Biovail Corporation, Manufacturing Division/ Canada: manufacturer of the finished product and Innopharm Inc/Canada: company performing quality control of batches), the RMS has accepted copies of the licence granted by the Canadian Health Inspectorate of Canada (with which the EEA has a Mutual Recognition Agreement for their own territories) including confirmation that acceptable standards of GMP are in place at those non-Community sites as certification that acceptable standards of GMP are in place at those non-Community sites.

GMP active substance
Regarding the statements on GMP for the active substance a statement is provided from the manufacturer responsible for batch release situated in the EU (i.e. Glaxo Wellcome GmbH&Co./Germany).

Active substance and excipients

The active substance is bupropion hydrochloride, an established active substance described in the USP. Two manufacturers of the active ingredient are included in the dossier.

The active substance specification is considered adequate to control the quality and meets the requirements of the current USP monograph on bupropion HCl. The control in this monograph on related substances (by USP Tests 1 [TLC] and 2 [HPLC] cover an extended range of impurities. Batch analytical data demonstrating compliance with this specification have been provided by both suppliers for six and five batches, respectively.

Both suppliers have used the Active Substance Master File (ASMF) procedure for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product and the quality and quality control of the active substance. Competent Authorities thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance use in the medicinal product.

All the excipients comply either with USP or Ph.Eur. substances, or with appropriate in-house specifications. Ph.Eur. and USP are official handbooks (pharmacopoeias) in which methods of analysis with specifications for substances are laid down by the authorities of the USA or EU, respectively.

Medicinal Product

Dose form

The product concerns modified release tablets. The official standard term of these tablets is prolonged release tablets. However as in most Member States other bupropion hydrochloride containing prolonged release tablets are already on the market with a different release profile:
- Zyban for the indication smoking cessation
- and in some countries Wellbutrin SR for the indication Major depressive episodes (twice daily dose),
it was accepted to use the term "modified release tablets" for Wellbutrin XR. However, this issue was forwarded to the EDQM for further discussion (See below Follow up measures).

Composition

The product concerns modified release tablets containing 150 respectively 300 mg bupropion hydrochloride.

The tablet consists of the following excipients:

*Tablet Core: Polyvinyl Alcohol, Glyceryl Dibehenate

*Tablet Coating:

First coating: ethyl cellulose, Povidone K-90, Macrogol 1450,

Second coating: Macrogol 1450, Methyl Acid Ethyl Ecrylate Copolymer Dispersion Eudragit L30 D-55, Silicon dioxide Triethyl Citrate Black Printing Ink (Opacode S-1-17823).

*Printing Ink: Black Printing Ink (Opacode S-1-17823). Opacode S-1-17823 consists of Shellac Glaze ~45% (20% Esterified), Iron Oxide Black (E172) and Ammonium Hydroxide 28%.

Container/closure system

White opaque high density polyethylene (HDPE) bottles containing a combination charcoal/silica gel desiccant canister and closed with a child-resistant closure that includes an induction heat seal membrane.

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The tablets are diffusion controlled tablets consisting of a tablet core surrounded by release controlling and moisture barrier coatings. These coatings form a membrane that is responsible for controlling the release of Bupropion Hydrochloride *in-vivo*.

The selection of the excipients is based on early compatibility studies and formulation studies. All excipients are commonly used in the manufacture of medicinal products and sufficient information on the quality of the excipients has been provided. All excipients are known pharmacopoeial substances with exception of the proprietary printing ink mixtures.

Manufacturing process and quality control of the medicinal product

The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product has been presented in accordance with the relevant European guidelines. For the batch size a range has been given, this is acceptable.

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification is based on the monograph for modified-release tablets in the Ph. Eur. and includes tests for appearance, identity, uniformity of content, dissolution, assay and residual solvents. The absence of release specifications on related substances for the finished product is accepted taking into account the low levels of impurities present at release. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.
For the dissolution specification, different dissolution specifications for each strength are accepted for the 4 and 8 hour points.

Satisfactory validation data for the analytical methods has been provided.

Batch analytical data from the proposed production site has been provided, demonstrating compliance with the specification.

Stability tests on the finished product
Stability data on the product has been provided from three batches for each strength in accordance with applicable European guidelines demonstrating the stability of the product for 18 months. No specific storage conditions need to be included in the SPC or on the label. Additional storage label: Store in the original container in order to protect from humidity and light.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies:
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded..

II.2 Non clinical aspects

General remark

Most of the non-clinical studies included in this application are the same as those submitted and assessed in the MAA for Zyban. Only those studies which have not been assessed already for Zyban are critically assessed during the assessment of Wellbutrin XR dossier. These concern in vitro studies on action potential, some additional pharmacokinetic studies, and juvenile toxicity studies. In addition, potential differences in the non-clinical safety assessment related to the longer duration of administration of Wellbutrin XR as compared to Zyban have been assessed.

Good Laboratory Practice

Many of the earlier non-clinical studies predate the implementation of GLP regulations. However, the quality of the reports was considered sufficient to facilitate a proper evaluation and the validity of the studies was not compromised by comparison of these data with those from the recently performed studies or other discrepancies. Therefore the lack of GLP for the earlier studies was accepted.

Pharmacology

Bupropion contains one chiral centre and is marketed as a racemic mixture of the enantiomers.
The parent compound and its active major metabolites (hydroxybupropion and threohydrobupropion) are selective catecholamine reuptake inhibitors. Bupropion and hydroxybupropion also inhibit firing rates of noradrenergic neurons in the locus ceruleus and dopaminergic neurons in the substantia nigra and ventral tegmental area. In addition, at doses that do not increase locomotor activity, bupropion, its resolved enantiomers, and its active major metabolites are active in various animal models commonly used to predict antidepressant activity in humans.
The in vivo pharmacological activity of the individual enantiomers was not significantly different from that of racemic bupropion regarding antidepressant activity.

Non-clinical studies show that plasma hydroxybupropion concentrations reach a level, were they could interfere with the action potential, notably causing a shortening of the action potential duration. This could be of clinical significance at the supratherapeutic plasma concentration range.

Pharmacokinetics

A range of absorption, pharmacokinetics, distribution, metabolism, and excretion studies have established the fate of bupropion in the animal species used for the safety evaluation of the drug. These studies showed that both rats and dogs, the main animal species used in the toxicological evaluation of bupropion, were exposed to a similar range of metabolites as humans. However, the level of exposure to threohydrobupropion was higher in humans than in the animal species. Furthermore, plasma concentrations of bupropion in pharmacokinetic bridging studies were lower in animals after repeated doses than after a single dose, suggesting that bupropion induces its own metabolism in each animal species examined; a phenomenon not seen in humans at relevant clinical doses. Therefore, AUC values for the parent drug in mice, rabbits, and dogs were lower (0.04- to 0.8-fold) than the corresponding values in humans, and AUC values in rats (female) were about 3-fold higher. When comparing C_{max} values – probably in this case a better indicator for the acute adverse effects (convulsions, ataxia, mortality) – the exposure multiples are greater [human steady state Cmax after 300 mg bupropion XL: 161 ng/mL; dog 2-fold; rat male 4-fold, female 23-fold; rabbit 7-17-fold; mouse male 7-fold, female 1.1-fold].

After the submission of additional study reports on the metabolism of bupropion, it was concluded that these data do not raise additional issues of potential pharmacokinetic interactions.

Toxicology

Bupropion, in single and repeated dose toxicity studies, produced ataxia, convulsions, and mortality which were a limiting factor to evaluating higher doses in animals. Mortalities occurred at doses much higher than those proposed for clinical use and therefore the mortality observed in these studies is unlikely to be of any clinical relevance.
Convulsions were seen in mice and rats at doses ≥100 mg/kg/day, in rabbits (organogenesis evaluation) at ≥100 mg/kg/day, and in one dog at 150 mg/kg/day (highest dose evaluated), but were not observed in juvenile rats at doses up to 346 mg/kg/day (highest dose evaluated). Seizures have been seen in humans at an incidence of 1 in 1000 at a dose of up to 400 mg/day Wellbutrin SR® and Wellbutrin XL®, confirming the suitability of the animal models for predicting this particular hazard.
The predominant changes following repeated administration occurred in the liver (liver weight increase, hepatocellular hypertrophy, and nodular hyperplasia) as would be expected from an enzyme inducer. In mice, rats, and dogs the pattern of changes were similar and in general reversible. At the maximum recommended dose in humans there is no evidence of any enzyme induction (see II.3 clinical aspect), which suggests that the hepatic findings in the laboratory animals have only limited relevance to risk assessment in humans in this respect.
Bupropion did not cause adverse effects on fertility, general reproductive performance, or lactation ability in rats. No fetal abnormalities were observed in the mouse, rat, or rabbit. There were no effects on the development or behaviour of F1 generation mice, on overall reproductive performance of F0 or F1 generation rats, or on development or behaviour of F1 generation rats. Additionally, bupropion did not cause adverse effects on viability, clinical observations, physical development, neurobehavioral function,

or fertility in juvenile rats or there were any new toxicities seen previously not documented in the adult animals.
In genetic toxicology studies, bupropion produced borderline positive results in Ames assays. Bupropion was not clastogenic in cultured human lymphocytes and was negative in the mouse lymphoma assay, and in the in vivo liver UDS assay. Although some activity was seen in an in vivo chromosome aberration test, two further studies were unable to repeat the positive findings of the first assay which casts doubt upon their relevance. In addition, threohydrobupropion was not mutagenic in Ames assays or clastogenic in cultured human lymphocytes. In conclusion, the genotoxicity data indicates that bupropion is a weak bacterial mutagen; it is not a mammalian mutagen and, as such, is unlikely to be of concern as a human genotoxic agent.
Both bupropion carcinogenicity studies (mice and rats) were negative. The changes seen in the liver as described for bupropion in the rat carcinogenicity study were the result of long-term enzyme induction which resulted in hypertrophy, hyperplasia, and eventually nodular hyperplasia in the liver. Hepatic enzyme induction was not seen in humans treated with bupropion (see II.3 clinical aspects) and the rodent findings were considered to be specific to these animals only.
Based on all of the above information, it is concluded that bupropion is not carcinogenic in mice or rats and is not considered harmful to humans at the recommended therapeutic dose.
Both induction-related limiting of exposure in toxicology studies and dose limiting overt pharmacology in the form of CNS-related clinical signs (convulsions) impacted the magnitude of margins of safety based on total drug exposure (AUC). In view of the relatively low exposure in the animal studies the safety has largely to be based on the available clinical (post-marketing) data, including the (lack of) carcinogenic potential. (See at the end of this PAR: Follow up measures).

Environmental risk assessment
Bupropion hydrochloride is already authorised for many years as Zyban.
The environmental risk assessment is incomplete, but the applicant has indicated that lacking data will be generated. It is considered acceptable that this will be done as a follow-up measure. (See at the end of this PAR: Follow up measures).

II.3 Clinical aspects

Quality of clinical studies, compliance with GCP
The formulation of the batch used in key (European) clinical studies is identical to that proposed for marketing (with the exception of the printing on the tablets).
The RMS has been assured that GCP standards were followed in an appropriate manner in these key clinical studies conducted.
Additionally the dossier contained studies performed with the SR formulation and immediate release formulation.

Clinical Pharmacology

Pharmacokinetics

This is a full application dossier. All relevant pharmacokinetic studies were submitted, including studies with IR and SR tablets (Zyban). The Wellbutrin XR tablets (in the studies noted as XL tablets) have not been submitted as a line extension of the registered SR tablets. Almost all of the submitted studies for the application of Zyban have also been submitted for this application. Therefore the assessment of Zyban has been taken into account, in addition to the newly submitted studies for this application. The new studies are discussed separately. The studies submitted both for Zyban and for this application are evaluated/discussed in separate sections.

Newly submitted studies:

Bupropion is absorbed through the whole gastro-intestinal tract, and absorption was only in the colon about 25% lower than in the rest of the gastro-intestinal tract. Food (standard high fat breakfast) had no clinical significant effect on the bupropion pharmacokinetics after administration of the XL tablets, this was also observed for Zyban.

A comparable exposure of bupropion and its metabolites is observed after once daily administration of the 300 mg XL tablet compared to thrice daily administration of the 100 mg IR tablet. AUC, C_{max} and C_{min} are just inside or below the lower boundary of the 0.80 – 1.25 90% CI acceptance range. The data indicate the slower release properties of the XL tablet, with a delay in T_{max} and as shown in the C-t curve an increase in the (apparent) elimination half-life. The results obtained for the XL tablet are in line with those obtained for the SR tablet (Zyban).

A comparable exposure of bupropion and its metabolites is observed after single dose administration of the 150 mg SR (Zyban) and XL tablet, as well as after once daily administration of the 300 mg XL tablet compared to twice daily administration of the 150 mg SR tablet.

Bupropion increased the AUC and Cmax of citalopram, a substrate of CYP2C19 and CYP2D6, approximately 40 and 30%, respectively. Citalopram did not affect the pharmacokinetics of bupropion.

Bupropion and hydroxybupropion exposure decreased by about 65 and 80%, respectively, due to the inducing effects of ritonavir (600 mg b.i.d.). In addition, also the exposure to threohydrobupropion and erythrohydrobupropion decreased by about 50 and 70%, respectively.

Zyban studies:

After oral administration of bupropion 150 mg as an IR formulation maximal bupropion plasma concentrations of approximately 200 ng/ml were observed after about 1.5 h (=T_{max}). AUC and Cmax values increased dose-proportional over the dose range 12.5 – 200 mg. The absolute bioavailability of bupropion is not known, but recovery data in urine indicate that bupropion is absorbed for at least 87%. Concomitant intake with food has no influence on the rate and extent of absorption. Cmax values of the active metabolite hydroxybupropion were 1.5 – 4 fold higher (molar base) when compared with Cmax values of bupropion and AUC values 12 – 17 fold higher. For the metabolite threohydrobupropion Cmax levels were similar and AUC values approximately 4 fold higher than those of bupropion. The diastereoisomer of threohydrobupropion, erythrohydrobupropion, could not be detected after single dosing.

After administration of bupropion as an SR tablet Cmax values were statistically significant lower for bupropion (approximately 55%), hydroxybupropion (approximately 20%) and threohydrobupropion (approximately 30%), compared with the IR tablet, due to a slower release of bupropion from the SR tablet (delay in T_{max} with approximately 85%, resulting in a T_{max} for the SR tablet of 2.5-3 h). The apparent half-life of bupropion increased into approximately 20 h. AUC and Cmax increased dose proportional over the dose range of 100 to 300 mg. As observed after dosing with the IR formulation, Cmax values of hydroxybupropion were approximately 3 fold higher (molar base) than bupropion and AUC values approximately 14 fold higher. For threohydrobupropion Cmax levels were similar and AUC values approximately 5 fold higher compared with bupropion.

At steady state lower Cmax values and a lower fluctuation index were observed for bupropion from the SR tablet (2 times daily 150 mg) compared with the IR tablet (3 times daily 100 mg). AUC, C_{min} and Cav were similar. No differences were observed in the steady state pharmacokinetic parameters of the metabolites

after administration of the SR and IR tablet. This was also observed for the erythrohydrobupropion metabolite which has similar levels than those of bupropion.

Protein binding of bupropion, hydroxybupropion and threohydrobupropion is moderate (approximately 84, 77 and 42%, respectively) and interactions arising from displacement are expected not to be clinically relevant. Bupropion is metabolised in the liver into the active metabolite hydroxybupropion primarily by CYP2B6 and to a lesser extent by CYP1A2, 2A6, 2C9, 2E1 and 3A4. An in vivo study with cimetidine, a cytochrome P450 inhibitor showed no clinically relevant interaction. In vivo studies with a CYP2B6 inhibitor are not carried out, as these studies are not feasible in healthy volunteers. Specific CYP2B6 inhibitors which are therapeutically used in humans are not known. Orphenadrine is not a good candidate, because it is not clearly known to be a specific inhibitor of CYP2B6. At therapeutic doses orphenadrine plasma concentrations were lower than 1.5 µM (See *Labout JJM, Thijssen CT, Keijser GGJ, and Hespe W. Difference between single and multiple dose pharmacokinetics of orphenadrine hydrochloride in man. Eur. J. Clin. Pharmacol. (1982) 21:343-350*). This concentration is much lower than the lowest concentration (20 µM) used in in vitro studies, at which the formation of hydroxybupropion was inhibited by approximately 14%. Therefore orphenadrine is not suitable to be used as an inhibitor of CYP2B6. Also a study with substrates of CYP2B6 would be difficult to carry out, because the two known substrates for which CYP2B6 is considered an important metabolic pathway are iphosphamide and cyclophosphamide. As these compounds are antineoplastic agents, studies cannot be conducted in volunteers.

Taken into account that approximately 30% of the metabolism of bupropion occurs by the pathway in which CYP isoenzymes are involved, the impact of inhibition of this pathway is not considered to lead to safety problems. Moreover, other pathways can compensate the eventual inhibition of the CYP pathway.

The active isomers threohydrobupropion and erythrohydrobupropion are formed by carbonyl reduction of bupropion through carbonyl reductase. Non-enzymatic cleavage of the sidechain of bupropion results in the formation of the non-active meta-chlorobenzoic acid, which is further converted into its glycine conjugate.

Bupropion showed in vitro a minor inhibitory effect on CYP2C9, 2E1 and 3A4, with an IC50 > 30 µM, and a more predominant effect on CYP2D6 (Ki: 21 µM). Hydroxybupropion showed only an inhibitory effect on CYP2D6, with a Ki of 13.3 µM. An in vivo interaction study with desipramine, which is a substrate of CYP2D6, showed an increase in the AUC and Cmax of desipramine of approximately 5 and 2-fold, respectively.

After administration of radioactive labelled bupropion approximately 87% of the radioactivity could be recovered in the urine and approximately 10% in faeces.

The pharmacokinetics of bupropion and its metabolites were similar in non-smokers and smokers and were not affected by age or by moderately impaired liver function. The influence of renal function on the pharmacokinetics of bupropion was not studied. As the renal clearance accounts for less than 1% of the total clearance of bupropion, it is unlikely that the overall elimination of bupropion, itself, would be affected in case of renal failure. Elimination of metabolites may be reduced in patients with renal failure, but due to the multiple pathways for elimination (including metabolism and renal excretion), it is unlikely that this will lead to large changes in the pharmacokinetics of these metabolites. Therefore, the SPC conservatively describes the administration of bupropion to patients with renal impairment.

Pharmacodynamics

Bupropion hydrochloride is an aminoketone. Bupropion is a selective inhibitor of the neuronal re-uptake of noradrenaline and dopamine with minimal effect on the re-uptake of serotonin, and does not inhibit monoamine oxidase. While the mechanism of action of bupropion, as with other antidepressants, is unknown, it is presumed that this action is mediated by noradrenergic and/or dopaminergic mechanisms.

The pharmacodynamic profile of bupropion is well known from Zyban and sufficiently covered in the SPC.

Dose response study(ies)

No formal dose response studies were conducted for the XL formulation. The company, however, conducted exploratory analysis investigating efficacy at 150mg and 300mg.

A linear dose response relationship may be considered as proof of efficacy. Moreover, a dose response study may be the substantiation for the optimal dosage(s). As no formal dose response study has been conducted with bupropion XL, a statement about these events cannot be made. On the other hand most dose response studies conducted in MDD show a flat distribution between dosages.

The submitted dose response studies, **Studies 203, 205 and 212,** were not conducted with XL formulation but with the SR formulation. In **study 203** both 150 and 300 mg separated from placebo. **Study 205** produces inconsequent results: Low dosage bupropion SR (100 mg) was able to separate from placebo while higher dosages did not. In **Study 212** the results from the two dosage bupropion SR (50-150 mg and 100-300 mg) were presented as one. Therefore a statement about an eventual dose response effect cannot be made based on the results presented.

In the US studies conducted with bupropion XL, higher dosages were used in the placebo-controlled studies as compared to the EU studies.
The dosage used in the long-term studies was 300 mg. The reason for this is that prior to the initiation of the three EU studies (AK130939, AK130940, WXL101497), scientific advice was given about the extended-release bupropion for depression development programme. As part of the discussion the MEB advised the applicant on several aspects of study design including the dosages to be used. The advice was that the maximum daily dose in the depression studies should not exceed 300mg. The rationale behind this advice was that sustained-release bupropion already has been approved in the EU as an aid to smoking cessation (as Zyban) and the maximum daily dose permitted is 300mg because of a possible increase of the risk of seizures.
The currently approved maximum daily dose in the USA is 450mg for Wellbutrin XL and 400mg for Wellbutrin SR. The applicant believes that these higher doses are both efficacious and tolerable but decided to follow the advice of the MEB and limited the dose in the clinical studies to 300mg per day.

Clinical Efficacy

Short-term efficacy

Short-term placebo-controlled studies with bupropion XL (= Wellbutrin XR), bupropion SR (Wellbutrin SR or Zyban) and bupropion IR (Wellbutrin) have been submitted. Short-term efficacy has been proven. This is mainly based on additional analyses in responders/remitters which were made comparing the response/remission rates for bupropion treatment versus treatment with an SSRI or SNRI (venlafaxine). These data demonstrate that the response/remission rates show no differences between the bupropion treatment groups and SSRI treatment group.
Furthermore, the MEB has taken into account the fact that for many years bupropion has been granted a licence for the indication MDD bupropion in several countries for many years.

Short-term placebo-controlled studies with bupropion XL.

See table 1 for an overview of the results.

The company conducted 3 EU short-term placebo controlled studies **(studies 101497, 130939 and 130940** in elderly patients) with a duration varying from 8-10 weeks. **Studies 101497 and 130939** were three-arm studies with venlafaxine 75-150 mg as third arm.
The patients included in the studies were having a depressive episode with symptoms fulfilling to the DSM IV criteria.The HAMD/MADRS baseline scores indicate moderate depression.

Study 101497 is a positive study showing statistically significant differences on the primary outcome measures in favour of both bupropion XL 150-300 mg and venlafaxine 75-150 mg as compared to placebo.
Study 130939 shows statistically significant differences on the primary outcome measures for venlafaxine 75-150 mg as compared to placebo while bupropion XL 150-300 mg did not separate from placebo. This study should be considered as a negative study for demonstrating efficacy of bupropion XL 150-300 mg in MDD.
Also in the elderly **study 130940** bupropion XL 150-300 mg did not separate from placebo on the primary outcome measure for the ITT population LOCF(Last Observation Carried Forward) analysis. Therefore, in first instance, also the results from this study were considered as negative for proof of efficacy. The company, however, explained that the negative result was due to outliers predominantly in the placebo group whose MADRS scores had improved dramatically (between 15 and 30 points improvement from baseline) just prior to their withdrawal from the study. Moreover, a post-hoc analysis using another statistical approach demonstrated a statistically significant difference for the ITT population (LOCF analysis). This result was supported by the Observed Cases (OC) analysis and other secondary datasets. In summary, the elderly study shows in the OC analysis a statistically significant difference in favour of bupropion XL compared to placebo, while the LOCF analysis did not. In fact the study should be considered as failed (lack of assay sensitivity), but the applicant suggests that the LOCF analysis was not appropriate and this was confirmed by three “independent” experts: a statistical suggestion is suggested to overcome the problems of lack of assay sensitivity. The applicant suggests study AK 130940 should be considered as positive or, at worst, highly supportive for the efficacy of bupropion in the treatment of MDD. The discussion about the interpretation of the results of this study is bilateral (lack of assay sensitivity versus inappropriateness of ANCOVA analysis in case of no normal distribution in one of the treatment arms, using secondary outcome measures/analysis) but the results of this study are in any case not unsupportive for short-term efficacy. However, based on the results of this study, it cannot be stated that efficacy in the elderly population has been demonstrated unequivocally.

In **study 130931** the dosage bupropion XL was 300-450 mg (higher than the recommendation in the SPC). Moreover, the primary outcome measures (IDS and HAM-31) used in the studies were not comparable to the MADRS or HAM-D-17. However the applicant was able to recalculate the IDS and HAM-31 in HAMD-17 scores adequately, showing that study AK130931 and (the bupropion SR) studies AK 1A4001 and AK1A4002 (see further) were positive with regard to efficacy with a small magnitude of effect of about 2 points.
In **study 100368** bupropion XL (150-450 mg) was tested with the primary objective of measuring sexual functioning. In this study the HAM-D was used as secondary outcome measure.
Lack of placebo-control makes it difficult to assess this study. Compared to the other studies, a low response rate for venlafaxine was seen. No difference in efficacy was seen between venlafaxine and bupropion.
The same objective was chosen in **studies 130926** and **130927**. In these studies, bupropion XL 300-450 mg (higher than the recommended dosage) did not separate from placebo on the HAM-D. As escitalopram was also not superior to placebo in **study 130926,** this study should be considered failed while study 130927 is a negative study because only escitalopram was significantly superior to placebo.

Table 2: Overview of Efficacy results in the short-term placebo-controlled bupropion XL studies for the LOCF ITT population

Study/duration/ Continent	Treatments	N	Total Drop-out/ due to safety reasons/lack of efficacy (%)	Mean *MADRS*/ HAMD-17 at baseline	Mean *MADRS*/ HAMD-17 improvement from baseline	Magnitude of effect (mean improvement on the *MADRS*/HAMD-17)	Remission Rates (%)	Responder Rates (%)
101497 8 weeks EU	Placebo Bupropion XL 150-300 Venlafaxine 75-150	197 187 185	15 / 5/ 4 18/ 4/ 5 12/ 4/ 2	*30.4* *30.4* *30.0*	*-13.5* *-16.0* *-17.1*	 *-2.5 <-4,2, -0.7>** *-3.6 <-5.4, -1.8>**	32 47* 51*	46 57* 65*
130939 8 weeks EU	Placebo Bupropion XL 150-300 Venlafaxine 75-150	186 202 193	22/ 6/ 6 22/ 5/ 5 23/ 8/ 3	*30.6* *30.6* *30.1*	*-13.2* *-14.7* *-17.0*	 *-1.5 <-3.5, 0.5>* *-3.8 <-5.8, -1.8>**	38 45 56*	49 57 66*
130940 10 weeks elderly (mean age about 70 years) EU	Placebo Bupropion XL 150-300	204 210	22/ 11/ 4 23/ 8/ 5	*29.8* *29.5*	*-12.4* *-13.9*	 *-3.2 <-1.5> 0.2*		
Study 130931 8 weeks USA	Placebo Bupropion XL**300-450**	139 135	21/ 2/ 4 24/ 9/ 1	*MADRS*/ HAMD-17 Was not used	Significant difference on the IDS scale	--	27 41* on the IDS	45 53 on the IDS
100368 12 weeks USA Objective: Sexual functioning	Bupropion XL 150-**450** Venlafaxine 75-225	160 164	42/ 6/ 1 46/ 11/ 0	25.6 24.9	-12..9 -11.2	-2.65 < 1.03> 0.58	37 28	54 48
130926 8 weeks USAjective: Sexual functioning	Placebo Bupropion XL **300-450** Escitalopram 10-20 mg	127 135 144	20/ 5/ - 27/ 10/ - 27/ 3/ -	23.3 23.2 23.3	-11.9 -13.1 -12..9	--	38 46 42	51 63 62
130927 8 weeks USA Objective: Sexual functioning	Placebo Bupropion XL **300-450** Escitalopram 10-20 mg	130 134 133	28/ 5/ - 23/ 3/ - 24/ 5/ -	24.4 24.5 23.8	-12.1 -13.2 -14.2*	--	31 40* 49*	53 61 58*

Remission: MADR ≤ 11; Response: at least 50% improvement from baseline on the MADRS;
*: statistically significant superior to placebo

Short-term placebo-controlled studies with bupropion SR

Study 203 is a positive study showing statistically significant differences on the primary outcome measures in favour of both bupropion SR150 mg and bupropion SR 300 mg.
Study 205 produces inconsequent results: Low dosage bupropion SR was able to separate from placebo while higher dosages did not.
In **Study 212** bupropion SR 50-300 mg separated from placebo with a small magnitude of effect (on the MADRS). The relevance of the effects found in the studies mentioned in the above are very difficult to assess because of the lack of a third arm.
In study **AK studies (001, 002, 006, 007**) the primary objective was quality of orgasm and sexual functioning. The patients were suffering from MDD and the severity was measured during the studies. In **study AK 001** both bupropion SR 150-300 mg and sertraline 50-200 mg separated from placebo on the HAM-D 31. The applicant recalculated adequately the IDS and HAM-31 in HAMD-17 scores showing that studies AK 1A4001 and AK1A4002 (see below) were positive with a small magnitude of effect of about 2 points. Using this same outcome measure bupropion SR but not sertraline separated from placebo in **study AK 002**. In **studies AK006 and 007** both bupropion SR and fluoxetine were not superior to placebo. In **Study 209** bupropion SR 100-300 mg was compared to sertraline 50-200 mg. There was no difference at endpoint on the HAMD-31 (this was a non-placebo-controlled study).

The applicant presented an overview of the short-term efficacy study results which includes the re-analysis of data in terms of the HAMD-17. This overview indicates that the magnitude of effect of bupropion is about 2 points on the HAMD-17 which is rather small compared to other compounds that have been granted a licence for the MDD indication, but comparable with SSRIs.

Short-term placebo-controlled studies with bupropion IR

Many of the placebo-controlled bupropion IR studies (n =7) have major methodological flaws. In **studies 06 08, 09, and 14** patients who withdrew prior to day 21 were replaced. Only patients who were at least 14 days in the study were included in the efficacy analysis in **study 08.** In **study 09** patients were removed who failed to improve by at least 25% after 3 weeks. Therefore a statement about efficacy cannot be based on the results from these studies.
Moreover, the dosages used in many of the bupropion IR studies were much higher than the recommended dosage for bupropion XL in the treatment of MDD. In study 06: 300-600 mg, study 08: 300-750 mg, study 09 300-900 mg (in one arm), study 14: 300-600 mg, study 25: 300-450 mg.
Therefore only **studies 29 and 84** are worth reviewing: In **study 29** bupropion IR 150 mg and bupropion 300 mg did not separate from placebo (mean improvement from baseline on the HAMD-21), while in **study 84** bupropion IR 300 mg separated from placebo. The lack of a third arm, makes it difficult to make a statement of the relevance of the magnitude of effect.

Conclusion on short-term efficacy:
Additional analyses in responders/remitters were made comparing the response/remission rates for bupropion treatment versus treatment with an SSRI or SNRI (venlafaxine).
These data demonstrate that the response/remission rates show no differences between the bupropion treatment groups and SSRI treatment groups. The remission/response rate in the pooled placebo controlled studies was 40%/54% respectively 39%/52% for bupropion and SSRI's. However, the remission/response rate in the placebo controlled studies was 43%/53% in the bupropion group versus 52%/62% in the venlafaxine group. These figures indicate that in the pivotal placebo controlled studies bupropion is as effective as SSRIs but less effective compared to venlafaxine.
This has been confirmed by data showing that in the 'pivotal' placebo controlled studies (WXL101497, AK130939 and AK130940/elderly), the magnitude of the effect of bupropion is comparable to that of SSRI's, but less compared to venlafaxine.
Altogether, based on the data submitted, short-term efficacy for bupropion can be accepted. Furthermore, the MEB has taken into account the fact that bupropion has already been used for the MDD-indication in many countries for many years.
The results of the elderly study are at least not unsupportive for efficacy, but in fact the study should be considered as failed. Therefore the wording in the SPC concerning the elderly reads "*Efficacy has been*

shown equivocally in the elderly. In a clinical trial, elderly patients followed the same dose regimen as for the adults (see Use in Adults). Greater sensitivity in some elderly individuals cannot be ruled out.".

Long-term efficacy:

One relevant long-term study was submitted:
Methodology: This was a multicentre, parallel, randomized, fixed dose, double-blind, placebo-controlled trial (**study 4004)** in outpatients diagnosed with moderate to severe recurrent major depression. A sufficient number of subjects were screened and enrolled in the Open-Label Phase to provide approximately 400 subjects who responded to treatment and entered the Double-Blind Phase. Subjects took 300mg/day of bupropion SR during the Open-Label Phase. Upon entering the Double-Blind Phase, subjects were randomized (1:1) to either bupropion 300mg/day or placebo.
The study lasted up to 53 weeks and consisted of three phases: Screen Phase (1 week duration), Open-Label Phase (8 weeks duration), and Double-Blind Phase (44 weeks duration). After giving informed consent, completing screening assessments, and meeting inclusion/exclusion criteria, all subjects entered a 1-week Screen Phase. Following completion of the Screen Phase, those subjects who continued to satisfy the inclusion/exclusion criteria requirements were enrolled in the Open-Label Phase. Clinic visits were conducted weekly during the 8-week Open-Label Phase. Subjects whose depression responded to treatment during the Open-Label Phase (defined as a CGI-I rating of 1 or 2 at each of the last 3 visits, namely Weeks 6, 7, and 8) were randomized to either bupropion XL or placebo in the Double-Blind Phase.
Criteria for evaluation: The primary endpoint of the study was the time to relapse/recurrence of depression as measured by the time from randomization into the Double-Blind Phase to the first prescription of pharmacotherapy or ECT determined by the investigator to be necessary for the treatment of a relapse/recurrence of depression.
Efficacy was evaluated by the 21-item Hamilton Rating Scale for Depression (HAMD), HAMD Depressed Mood Item (Item 1), the Hamilton Rating Scale for Anxiety (HAMA), and the Clinical Global Impressions Scales for Severity of Illness (CGI-S) and Improvement of Illness (CGI-I).
Safety was evaluated by assessing vital signs, weight, and adverse events. In addition, laboratory assessments were used to evaluate safety in the Double-Blind Phase.
Results: A statistically significant difference in favour of bupropion SR was seen when the survival curves for the two treatments groups were compared using both Wilcoxon (p=0.0041) and log-rank (p=0.0028) tests. In the double-blind phase, median time to relapse was Week 24/Day 168 for the placebo group. Median time to relapse for Wellbutrin is presumed to be greater than 44 weeks as this threshold was never met during the study.
Discussion: In this study the definition of "relapse/recurrence" has not been chosen well. The company has opted for the definition of "relapse/recurrence": first prescription of pharmacotherapy or ECT determined by the investigator. Scientific advice was given in the past in which the MEB clearly stated that the definition of the endpoints in this study was rather loose and that the company should consider the possibility of using a threshold value on a specific rating scale instead. This is in line with the CHMP depression guideline.
To address this issue the RMS suggested that the company should show whether the investigators defined relapse equally in both placebo and bupropion groups. To demonstrate whether the investigators defined relapse equally in both the placebo and bupropion groups or whether they were biased in some way, the company examined the HAMD-17 score for the bupropion and placebo groups at the point at which patients were considered to have a relapse (re-emerging of symptoms). The mean HAMD-17 scores at the point of withdrawal from the study were more or less similar indicating that although the relapse criteria were based on the investigator's judgement, no bias for or against bupropion was introduced.
Moreover, two analyses have been presented:
- relapse defined as investigator's assessed need for treatment or HAMD-17 total score above various cut-offs
- relapse defined by HAMD-17 Total score.

Both analyses show that the odds of placebo patients relapsing are consistently greater than those for bupropion treated patients. In the analysis which defined relapse as the earlier of the time at which a patient reached a particular cut off or the time at which the investigator determined that the patient should be withdrawn to receive treatment, statistical significance was shown for all HAMD cut offs assessed with odds ratios ranging from 1.59 to 1.74. The time to relapse for bupropion treated patients was at least twice as long as for placebo treated patients.
In the other analysis relapse was defined as a HAMD cut off regardless of the investigator assessment and patients who were withdrawn by the investigator before they reached the specified HAMD cut off were considered to be non-relapsed and their data were censored (i.e. counted in the denominator but not counted in the numerator as relapsers). The results of this analysis show that the proportion of relapsers was consistently higher in the placebo group than in the bupropion group (Odds ratios ranging from 1.07 to 2.81) although statistical significance was not reached. The lack of statistical significance in this latter analysis is not surprising as a large number of patients were withdrawn by the investigator before they reached the HAMD cut off. Such an analysis is only valid in a prospectively defined study and the fact that bupropion still shows a numerical benefit over placebo in this study, despite the large numbers of censored patients is encouraging.

Concerning the two analyses we agree with the company that the odds of placebo patients relapsing are greater than those for bupropion treated patients.

Conclusion on long-term efficacy
The new analyses support the original protocol defined analysis and maintenance of effect may be considered as demonstrated. However, this study does not allow any text for prevention of relapse in section 4.1 of the SPC (in accordance with SPCs for other antidepressants).
Nevertheless, in accordance with the SPCs for other authorised antidepressants (e.g. Seroxat) the following sentence "*Patients with depression should be treated for a sufficient period of at least 6 months to ensure that they are free from symptoms*" has been included.

Clinical Safety

The extensive data submitted seem to be sufficient to assess the safety profile of bupropion XL in the treatment of MDD. In this respect, reference is also made to the Article 36 Referral for Zyban (see EMEA website). During this referral safety data for bupropion were extensively discussed.

Given the different mechanism of action of bupropion it is not surprising that the safety profile is different compared to SSRI/SNRI's. Bupropion is a noradrenaline and dopaminergic re-uptake inhibitor and, unlike the SSRIs/SNRIs, does not have activity at post-synaptic receptors. Adverse events such as sexual dysfunction, sedation, fatigue and weight gain which occur frequently with the SSRIs/SNRIs do not occur significantly more frequently with bupropion than with placebo. On the other hand one may expect noradrenaline and dopaminergic adverse events with the use of buproprion. These AE's can be found in the current SPC: dry mouth, nausea and insomnia, abdominal pain, agitation, tremor and sweating. Abdominal pain, dry mouth, nausea agitation, insomnia, tremor, and sweating are dose related.
The long-term safety could only be assessed in the double-blind phase of the withdrawal study **(study 4004**). The most reported AE's were headache (placebo 13%, bupropion SR 16%), rhinitis (placebo 4%, bupropion SR 7%) and infection (placebo 5%, bupropion SR 10%). A statement about the relevance of the long-term safety profile of bupropion XL can not be made based on these results because of the lack of a third arm in this study.
As no formal dose response study has been conducted with bupropion XL, a statement about adverse events by dose cannot be made. However in the past the following dose related AE's were found: Abdominal pain, dry mouth, nausea agitation, insomnia, tremor, and sweating.

There seems to be no clinically relevant cardiovascular risk involved in using bupropion. This has been investigated properly and the SmPC covers all the eventual cardiovascular side-effects that may occur with the use of bupropion.

The available data concerning hypersensitivity are well analysed. Hypersensitivity reactions with bupropion may occur and are adequately described in the SmPC.

The available data concerning seizures are well analysed. In the past there was much concern about the incidence of seizures with the IR formulation. Indeed seizures with the use of bupropion may occur but the incidence with the SR and XL is not higher (0.06 vs 0.07) compared to other antidepressants. Moreover, the use of bupropion is contra-indicated in patients with a current seizure disorder and any history of seizures.

An obvious increase in risk for suicidal behaviour with the use of bupropion, when compared to placebo, is not shown for either MDD or non-MDD indications. Depression is listed in the Adverse Reactions section of the bupropion SmPC for all indications. For the depression indication, warnings regarding clinical worsening and suicide risk associated with psychiatric disorders are included in the proposed SmPC.

Because of the catecholaminergic action of bupropion a decrease in blood pressure (catecholaminergic action) or hypotension may be expected. This however was not found in the studies.
Although the incidence of AE's in elderly is comparable to that of placebo, still a greater sensitivity in some elderly cannot be ruled out.

A disadvantage of the SSRIs/SNRIs may be the discontinuation symptoms after discontinuation of therapy. The company demonstrated that the percentage of patients with discontinuation symptoms in the bupropion XL treatment group was comparable to that of the placebo treated patients during the taper phase (7% vs. 5% of the patients) and during the follow up (10% vs. 11%). In the venlafaxine group there were more patients suffering from discontinuation symptoms: taper phase 13%, follow-up phase 19%. Also in the elderly study there was no difference between both treatment groups (bupropion versus placebo) for patients with discontinuation symptoms. The long-term study also indicates that patients treated with bupropion XL may have less/no discontinuation symptoms after cessation. On the other hand data in animal studies a potential for abuse is suggested (See SPC), but (few) spontaneous reports suggest that the risk for abuse, dependence or addiction is very small (See SPC). The latter is also confirmed by some epidemiological long term studies and extensive European and US post-marketing surveillance data.

In the combined European and US studies short-term studies AEs leading to withdrawal were reported in 5% of bupropion XL patients, 4% of placebo patients and 5% of comparator (venlafaxine XR and escitalopram) patients. A similar pattern was seen in the short term bupropion SR and IR studies.
These figures indicate that, although the safety profile of bupropion XL in the short-term treatment may be different from other antidepressants, the tolerability is comparable to that of the SSRIs/SNRIs. In the elderly study and the long-term study no third arm was included. Therefore a statement concerning long-term tolerability compared to other antidepressants is not possible.
In addition the company stresses on the lack of sexual side effects with bupropion claiming that these side-effects effects are a common cause for poor compliance to long term treatment with antidepressants, especially after the patient achieves remission of depression. The company claims that "*this benefit of bupropion XL over the SSRIs and venlafaxine is important as the impact of antidepressant induced sexual dysfunction not only affects patients' quality of life but may actually interfere with recovery from an episode of depression*". This may be true but can only be demonstrated in long-term comparative studies. Unfortunately these long-term studies have not been conducted and therefore there is no evidence for this claim.
The post-marketing experience is interesting, but by no means proves better tolerability compared to other antidepressants.

Concerning discontinuation symptoms: SSRI's and SNRI's have been associated with withdrawal reactions. The PEM (Prescription Event Monitoring) study in over 11,700 patients taking Zyban for smoking cessation did not give a signal for discontinuation symptoms but this was also the case in the PEM fluvoxamine, fluoxetine and sertraline studies. Moreover, the PEM study of bupropion has been conducted in a different population (smoking cessation patients).

In the clinical studies no difference was seen between placebo and bupropion in withdrawal symptoms using spontaneous reports. However, spontaneous reports as such do not allow to answer questions about the incidence of withdrawal symptoms.
Taking the above into account, the following text has been included in the SPC (section 4.2):
"Although discontinuation reactions (measured as spontaneously reported events rather than on rating scales) were not observed in clinical studies with WELLBUTRIN XR, a tapering off period may be considered. Bupropion is a selective inhibitor of the neuronal re-uptake of catecholamines and a rebound effect or discontinuation reactions cannot be ruled out."

Risk management plan
The identified and potential risks are the safety issues on which the referral to the CHMP based on article 36 for Zyban was started in 2002. These risks are seizures, hypersensitivity reactions, hypertension, arrhythmias and conductions disorders, myocardial ischaemia, cardiac failure, fatalities, suicidalities, withdrawal effects and pregnancy. Furthermore, due to the formulation there is the potential risk of medication error: There are three formulations of bupropion, immediate release to be administered thrice times daily, sustained release to be administered twice daily, and the current formulation which is an extended release formulation to be administered once daily.

The potential risk of carcinogenicity could not be sufficiently investigated due to CNS toxicity.
Taking into account the chronic use of bupropion for depression this should be investigated. The applicant committed to investigate the carcinogenicity of bupropion in the Henry Ford Health System using the standard validation procedure according to SEER Cancer Registry.
This seems reasonable. The power was calculated for patients with the diagnosis depression using bupropion and with the diagnosis depression. The minimum detectable relative risk seems correct and it seems possible to detect a risk if there is one. The company will use two datasets to increase the power of the carcinogenicity study thereby improving the minimum detectable cancer risk.

The risk management plan sufficiently covers the safety issues observed with bupropion. The main safety issues of bupropion have been investigated and monitored during the post-marketing period both in the US and the EU, therefore the SPC covers these safety issues sufficiently. It is agreed that at the moment the main potential risk is medication error due to the existence of more formulations of bupropion (administered either twice – Zyban/Wellbutrin SR - or once daily – Wellbutrin XR -) and the education and communication plan will be welcomed and looked forward to.

The applicant committed to submit an education and communication plan to the competent authorities concerning the avoidance of medication errors prior to launching the product.

The schedule for Periodic Safety Update Reports (PSUR) submission agreed at the end of the procedure is 6 monthly the first two years.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

The **chemical-pharmaceutical** dossier is in general of good quality. The product is approvable from a chemical-pharmaceutical point of view. Some follow up measures (FUMs) remain to be addressed after approval (see below).

The **non-clinical** dossier mainly consists of the non-clinical as those submitted and assessed in the MAA for Zyban (NL/H/191/01). Only those studies which have not been assessed for Zyban are critically assessed during the assessment of Wellbutrin XR dossier These concern in vitro studies on action potential, some additional pharmacokinetic studies, and juvenile toxicity studies. In addition, potential differences in the non-clinical safety assessment related to the longer duration of administration of Wellbutrin XR as compared to Zyban are discussed.
The conclusion of these assessments is that the pre-clinical dossier is acceptable.
However regarding the environmental risk assessment the applicant has indicated that lacking data will be

generated. It is considered acceptable that this will be done as a follow-up measure. (See below Follow up measures).

The **clinical** dossier is quite extensive and consists of studies related to three formulations of bupropion. For many years, bupropion has been granted a licence for the indication MDD in the USA, Canada and some EU accession countries, indicating that this compound is an effective treatment for depressive episode there. Moreover, the efficacy results point in the same positive direction (mean improvement from baseline, response).

Efficacy
To conclude on short term efficacy, the applicant has submitted data showing that in the 'pivotal' placebo controlled studies (WXL101497, AK130939 and AK130940/elderly), the magnitude of the effect of bupropion is comparable to that of SSRI's, but less compared to venlafaxine.
The interpretation of the results of the study in the elderly is bilateral (lack of assay sensitivity versus inappropriateness of ANCOVA analysis in case of no normal distribution in one of the treatment arms, using secondary outcome measures/analysis) but the results of this study are in any case not unsupportive for short-term efficacy.
Therefore the wording in the SPC concerning the elderly reads "*Efficacy has been shown equivocally in the elderly. In a clinical trial, elderly patients followed the same dose regimen as for the adults (see Use in Adults). Greater sensitivity in some elderly individuals cannot be ruled out.*"
Overall, based on these data, short-term efficacy for buproprion can be accepted.

In addition the post-hoc analysis for the long-term study, requested by the MEB, supports the original protocol defined analysis, by showing convincing results on symptom scores (IDS/HAM-D). Therefore maintenance of effect has been shown, and accepted. However, since maintenance of effect is a requirement for licensing a product for depression, the data do not allow any extra text for prevention of relapse in section 4.1 of the SPC. Nevertheless, in accordance with the SPC for other antidepressants the following has been included in section 4.2: "Patients with depression should be treated for a sufficient period of at least 6 months to ensure that they are free from symptoms."

Safety
The extensive data submitted seem to be sufficient to assess the safety profile of bupropion XL in the treatment of MDD. Overall, the approved SmPC sufficiently covers all safety issues.
Given the different mechanism of action of bupropion it is not surprising that the safety profile is different compared to SSRI/SNRI's.
There seem to be no clinically relevant cardiovascular risk with the use of bupropion.
The available data concerning hypersensitivity and seizures seem to be well analysed
There does not seem to be an obvious increase in risk for suicidal behaviour with the use of bupropion over that of placebo for either MDD or non-MDD indications. Nevertheless, a warning has been included in the SmPC.
As a result of the catecholaminergic action of bupropion a decrease in blood pressure (catecholaminergic action) or hypotension may be expected. This however was not found in the studies.
At the first instance it may seem that in the elderly the incidence of adverse events is comparable to that of placebo. However greater sensitivity in some elderly cannot be ruled out.
Although the data do not give an indication for the incidence of withdrawal symptoms and the clinical studies do not show a difference between placebo and bupropion in withdrawal symptoms measured as spontaneous reports, the following text has been included in the SPC (section 4.2):
"Although discontinuation reactions (measured as spontaneously reported events rather than on rating scales) were not observed in clinical studies with WELLBUTRIN XR, a tapering off period may be considered. Bupropion is a selective inhibitor of the neuronal re-uptake of catecholamines and a rebound effect or discontinuation reactions cannot be ruled out."
The tolerability seems comparable to that of the SSRIs/SNRIs. In the elderly study and the long-term study no third arm was included. Therefore a statement concerning with regard to long-term tolerability compared to other antidepressants is not possible. The post-marketing experience is interesting, but by no means proves better tolerability compared to other antidepressants.

The proposed **risk management plan** sufficiently covers the safety issues observed with bupropion. The main safety issues of bupropion have been investigated and monitored during the post-marketing period both in the US and the EU, therefore the SPC covers these safety issues sufficiently. It is agreed that at the moment the main potential risk is medication error and the education and communication plan will be welcomed and looked forward to. The applicant agrees to submit an education and communication plan to the competent authorities concerning the avoidance of medication errors due to the existence of two formulations of bupropion (administered either twice daily – Zyban/ Wellbutrin SR - or once daily - Wellbutrin XR-) prior to launching the product. (See below clinical follow up measures.)
Additionally the applicant submitted a proposal for a cohort study to investigate the carcinogenicity of bupropion in the Henry Ford Health System using the standard validation procedure according to SEER Cancer Registry post approval. The power was calculated for patients with the diagnosis depression using bupropion and with the diagnosis depression. The minimum detectable relative risk seems correct and it seems possible to detect a risk if there is one. The company will use two datasets to increase the power of the carcinogenicity study thereby improving the minimum detectable cancer risk (See below clinical follow up measures.)

Therefore based on all efficacy data submitted (including the additional analyses performed), it can be concluded that the magnitude of effect is small, but present and comparable to SSRIs.
Taking into account a well known safety profile for bupropion (Wellbutrin/Zyban), the fact that all short-term studies point in the same positive direction and maintenance of effect has been shown, and that for many years bupropion has been granted a licence for the indication MDD in the USA, Canada and some EU accession countries, indicating that bupropion is an option for treating major depressive episodes, the benefit/risk ratio for this product can be regarded positive.

In the Board meeting of 26 October 2006, the assessment reports were discussed. The minutes of this meeting will be published on the MEB's website.

The MEB, on the basis of the data submitted, considered that Wellbutrin XR demonstrated adequate evidence of efficacy for the approved indication(s) as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation. The other Member States mutually recognised the Dutch evaluation for the marketing authorisation.

There was no discussion in the CMD(h). Agreement between Member States was reached during a written procedure.

During the procedure there was a discussion on the definition of the pharmaceutical form. As stated in chapter II.1 (Quality) the applicant proposed to use the definition modified release tablets from a safety point of view. This was supported by the RMS and most CMSs. However one CMS did not agree with this proposal and was of the opinion that the definition in accordance with the EU standard terms should be used, i.e. prolonged release tablet. This CMS was prepared to temporarily accept this term, provided that this issue was forwarded to the EDQM for discussion, which was supported by another CMS. (See below Follow up measures).

At the end of the procedure there was also a discussion with one CMS whether information on the clinical efficacy data (placebo controlled studies) should be included in section 5.1 of the SPC. According to the SmPC guideline this section should only be used for clinical data if it relates to a new therapeutic area or if the results are clinically compelling. Furthermore, it would be difficult to summarise the data of all clinical studies performed (with all presentations) sufficiently succinctly in this section. Although the RMS believes that this information should be included in the Public Assessment Report (instead of the SPC) it was agreed that a type II variation would be submitted after finalisation of the procedure to include appropriate wording regarding the placebo controlled studies performed with bupropion. (See below Follow up measures).

The SmPC, PL and packaging fulfil the legal requirements and Braille conditions are met by the applicant. User consultation revealed that the PL fulfils the criteria in the readability guideline.

The schedule for Periodic Safety Update Reports (PSUR) submission agreed at the end of the procedure is 6 monthly the first two years (first PSUR to be submitted in August 2007).

The following **follow up measures** – FUMs - (post approval commitments) have been agreed during the procedure:

Area	Description
Quality	One of the AIM will test the starting material for precursors of some impurities. If these are found in the starting material, they will be controlled at a suitable level,-
Quality	A commitment has been made to provide 6 months accelerated stability data on two industrial batches of drug substance.-
Quality	A commitment has been made to apply Ph. Eur. 2.9.40 Uniformity of Dosage Units (Mass Variation) on the first three batches destined for the European Union-
Quality	A commitment has been made to update ASM DMF sections following acceptance of the responses. These will be submitted when available.-
Quality/pharmaceutical form	It has been agreed that the pharmaceutical form (modified release tablet) will be referred to the EDQM Standard Term Group to make a decision regarding the use of modified-release tablet as standard term in this particular case. The company will comply with the decision made by the EDQM.
Non clinical	A commitment has been made to undertake a fish ELS study and the Daphnia reproduction study and to incorporate the data generated into an updated Expert Report on Environmental Risk Assessment, to complete the ERA. Study reports and the updated Expert Report should be submitted within one year after MA approval
Clinical (RMP)	GlaxoSmithKline will submit an education and communication plan to the competent authorities concerning the avoidance of medication errors prior to launching the product.
Clinical (RMP)	The MAH has committed to perform a post-marketing study, using two datasets, to investigate carcinogenicity with the Henry Ford Health System using the SEER (Surveillance Epidemiology End Results) Cancer Registry procedure.
Clinical (SPC)	The MAH has committed to submit a type II variation after finalisation of the procedure (approximately 30 days) to include in the SmPC (section 5.1) appropriate wording regarding the results of the placebo controlled studies with bupropion in major depression.

List of abbreviations

AEs	Adverse events
ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
b.i.d.	bis in die (two times daily)
BP	British Pharmacopoeia
CMS	Concerned Member State
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products, CMD(h),
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
ERA	Environmental Risk Assessment
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
MDD	Major Depressive disorder
OC	Observed cases
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
PEM	Prescription Event Monitoring
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
PSUR	Periodic Safety Update Report
RMS	Reference Member State
SD	Standard Deviation
SNRIs	Serotonin Norepinephrine re-uptake inhibitors
SPC	Summary of Product Characteristics
SSRIs	Selective serotonin re-uptake inhibitors
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States