The European Agency for the Evaluation of Medicinal Products
Post-authorisation Evaluation of Medicines for Human Use

London, 28 November 2002
CPMP/27610/02

COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP)

OPINION FOLLOWING AN ARTICLE 36 REFERRAL

Bupropion hydrochloride

International Non-Proprietary Name (INN): **Bupropion**

BACKGROUND INFORMATION

Bupropion is a selective inhibitor of the neuronal re-uptake of catecholamines (noradrenaline and dopamine) with minimal effect on the re-uptake of indolamines (serotonin). Its mode of action in smoking cessation is not entirely understood.

In the European Union, bupropion containing medicinal products were authorised as an "aid to smoking-cessation in combination with motivational support in nicotine-dependent patients" through a Mutual Recognition Procedure (MRP) with the Netherlands as Reference Member State (RMS). Since licensing, concerns were raised in relation to the reports of suspected adverse drug reactions (ADRs) received associated with the use of bupropion containing medicinal products, particularly those of seizure and fatalities.

On 19 February 2002, Germany triggered a referral to the EMEA under Article 36 of Directive 2001/83/EC.

Germany requested the CPMP to give an opinion on whether the marketing authorisations of bupropion containing products indicated as "aid to smoking cessation in combination with motivational support in nicotine-dependent patients" should be maintained or changed in the terms of marketing authorisation or withdrawn, based on the reported serious suspected adverse reactions associated with these products, in particular reports on depression, suicidal ideation, suicide, seizures, undesirable cardiovascular effects, and angioedema, which raise potential public health concerns.

The referral procedure started on 22 February 2002. Written explanation was provided by the Marketing Authorisation Holders (MAHs) on 21 May 2002.

Based on re-evaluation of the currently available data, the majority of CPMP considered that the benefit/risk balance of bupropion containing medicinal products remains favourable for the current indication and adopted an opinion on 25 July 2002 recommending the maintenance of the Marketing Authorisations with amendments to the Summary of Product Characteristics as set out in Annex III. The CPMP recommended also that bupropion should be used in accordance with smoking cessation guidelines.

The Member States competent authorities will continue to keep the product under regular review, including follow-up measures, which have been submitted in the upcoming Periodic Safety Update Report.

The list of product names concerned is given in the Annex I. A summary of the scientific conclusions is provided in the Annex II together with the amended Summary of Product Characteristics in the Annex III.

The final opinion was converted into a Decision by the European Commission on 25 October 2002.

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ANNEX I

LIST OF THE NAMES, PHARMACEUTICAL FORM, STRENGTHS OF THE MEDICINAL PRODUCTS, ROUTE OF ADMINISTRATION, MARKETING AUTHORISATION HOLDERS, PACKAGING AND PACKAGE SIZES IN THE MEMBER STATES

BUPROPION CONTAINING MEDICINAL PRODUCTS WITH MARKETING AUTHORISATION IN THE MEMBER STATES

Member State	Marketing Authorisation Holder	Invented Name	Strength	Pharmaceutical Form	Route of administration	Packaging	Package size
Austria	GlaxoSmithKline Pharma GmbH, Albert-Schweitzer-Gasse 6, A-1140 Wien Tel: +431-97095-0 Fax: +431-97075198	Zyban	150 mg	Prolonged release tablets	Oral use	Blister (PA-Alu-PVC / Alu)	30,40,50,60, 100 tablets (in Austria available: 30 and 60 tablets)
Austria	Allen Pharmazeutika Gesellschaft m.b.H., Albert-Schweitzer-Gasse 6, A-1140 Wien Tel: +431-97095-0 Fax: +431-97075-170	Quomem	150 mg	Prolonged release tablets	Oral use	Blister (PA-Alu-PVC / Alu)	30,40,50,60, 100 tablets (all sizes in Austria presently not available)
Denmark	GlaxoSmithKline Pharma A/S, Nykær 68, DK-2605 Brøndby Tel: +45 36 759000 Fax: +45 36 753008	Zyban	150 mg	Prolonged release tablets	Oral use	Blister (PA-Alu-PVC / Alu)	100 tablets on the market. 30, 40, 50 and 60 tablets approved
France	Laboratoire GlaxoSmithKline 100 route de versailles 78163 Marly le Roi Tel: +33 1 39 17 97 70 Fax: +33 1 39 17 17 58	Zyban	150 mg	Prolonged release tablets	Oral use	Blister (PA-Alu-PVC / Alu)	30 ; 40 ; 50 ; 60 ; 100
France	Laboratoire GlaxoSmithKline 100 route de versailles 78163 Marly le Roi Tel: +33 1 39 17 97 70 Fax: +33 1 39 17 17 58	Quomem	150 mg	Prolonged release tablets	Oral use	Blister (PA-Alu-PVC / Alu)	30 ; 40 ; 50 ; 60 ; 100

Member State	Marketing Authorisation Holder	Invented Name	Strength	Pharmaceutical Form	Route of administration	Packaging	Package size
Germany	GlaxoSmithKline GmbH & Co. KG Leopoldstr. 175 D80804 München Tel: 0049-89-36044-0 Fax: 0049-89-36044-123	Corzen	150 mg	Prolonged release tablets	Oral use	Blister (PA-Alu-PVC / Alu)	100, 30, 60 (OP); 20 (UM)
Germany	GlaxoSmithKline GmbH & Co. KG Leopoldstr. 175 D80804 München Tel: 0049-89-36044-0 Fax: 0049-89-36044-123	Quomem	150 mg	Prolonged release tablets	Oral use	Blister (PA-Alu-PVC / Alu)	100, 30, 40, 50, 60 (OP); 30 (UM)
Germany	GlaxoSmithKline GmbH & Co. KG Leopoldstr. 175 D80804 München Tel: 0049-89-36044-0 Fax: 0049-89-36044-123	Zyban	150 mg	Prolonged release tablets	Oral use	Blister (PA-Alu-PVC / Alu)	100, 30, 40, 50, 60 (OP); 30 (UM)
Germany	GlaxoSmithKline GmbH & Co. KG Leopoldstr. 175 D80804 München Tel: 0049-89-36044-0 Fax: 0049-89-36044-123	Zyntabac	150 mg	Prolonged release tablets	Oral use	Blister (PA-Alu-PVC / Alu)	100, 30, 40, 50, 60 (OP); 30 (UM)
Greece	GlaxoSmithKline A.E.B.E 966 Kiphisias 15239 Chaland R Athens Tel: 6882100/6882958 Fax: 6847144/6847164	Zyban	150 mg	Prolonged release tablet	Oral use	Blister (PA-Alu-PVC / Alu)	30, 40, 50, 60, 100

Member State	Marketing Authorisation Holder	Invented Name	Strength	Pharmaceutical Form	Route of administration	Packaging	Package size
Ireland	Glaxo Laboratories Ltd., Stockley Park West, Uxbridge, Middlesex UB11 1BT, UK	Zyban	150 mg	Prolong release tablet	Oral use	Blister (PA-Alu-PVC / Alu)	30, 40, 50, 60 or 100 tablets. (but only 100 tablets are marketed)
Italy	Valda Laboratori Farmaceutici S.p.A. Via Zambeletti, 20021 Baranzate Di Bollate (Mi) Tel: 02 38061 Fax: 02 3501882	Corzen	150 mg	Prolonged release tablets	Oral use	Blister (PA-Alu-PVC / Alu)	30/40/50/60/ 100 Tablets
Italy	GlaxoSmithKline S.p.A. Via A. Fleming,2 37135 Verona Tel: 045 9218111 Fax: 045 9218388	Zyban	150 mg	Prolonged release tablets	Oral use	Blister (PA-Alu-PVC / Alu)	30/40/50/60/ 100 Tablets
Italy	Glaxo Allen S.p.A. Via A. Fleming,2 37135 Verona Tel: 045 9218111 Fax: 045 9218388	Quomen	150 mg	Prolonged release tablets	Oral use	Blister (PA-Alu-PVC / Alu)	30/40/50/60/ 100 Tablets
Belgium / Luxemburg	GlaxoSmithKline s.a./n.v. 13 Rue du Tilleul B-1332 Genval Tel: 0032 2 656 2111 Fax: 0032 2 656 2099	Quomem	150 mg	Prolonged release tablets	Oral use	Blister (PA-Alu-PVC / Alu)	30, 40, 50, 60, 100
Belgium / Luxemburg	GlaxoSmithKline s.a./n.v. 13 Rue du Tilleul B-1332 Genval Tel: 0032 2 656 2111 Fax: 0032 2 656 2099	Zyban	150 mg	Prolonged release tablets	Oral use	Blister (PA-Alu-PVC / Alu)	30, 40, 50, 60?, 100

Member State	Marketing Authorisation Holder	Invented Name	Strength	Pharmaceutical Form	Route of administration	Packaging	Package size
Netherlands	GlaxoSmithKline B.V. P.O. Box 780 3700 AT ZEIST/NL Tel: +31 30 6938100 Fax: +31 30 6938471	Zyban	150 mg	Prolonged release tablets	Oral use	Blister (PA-Alu-PVC / Alu)	30, 40, 50, 60 or 100 tablets
Netherlands	GlaxoSmithKline B.V. P.O. Box 780 3700 AT ZEIST/NL Tel: +31 30 6938100 Fax: +31 30 6938471	Quomem	150 mg	Prolonged release tablets	Oral use	Blister (PA-Alu-PVC / Alu)	30, 40, 50, 60 or 100 tablets
Netherlands	GlaxoSmithKline B.V. P.O. Box 780 3700 AT ZEIST/NL Tel: +31 30 6938100 Fax: +31 30 6938471	Corzen	150 mg	Prolonged release tablets	Oral use	Blister (PA-Alu-PVC / Alu)	30, 40, 50, 60 or 100 tablets
Netherlands	GlaxoSmithKline B.V. P.O. Box 780 3700 AT ZEIST/NL Tel: +31 30 6938100 Fax: +31 30 6938471	Zyntabac	150 mg	Prolonged release tablets	Oral use	Blister (PA-Alu-PVC / Alu)	30, 40, 50, 60 or 100 tablets
Portugal	Glaxo Wellcome Farmacêutica, Lda. PRT Rua Dr. António Loureiro Borges, 3, Arquiparque , Miraflores Algés Tel: +351 214 129 500 Fax: +351 214 121 857	Zyban	150 mg	Prolonged release tablets	Oral use	Blister (PA-Alu-PVC / Alu)	30, 40, 50, 60 and 100 tablets
Portugal	Glaxo Wellcome Farmacêutica, Lda. PRT Rua Dr. António Loureiro Borges, 3, Arquiparque , Miraflores Algés Tel: +351 214 129 500 Fax: +351 214 121 857	Zyntabac	150 mg	Prolonged release tablets	Oral use	Blister (PA-Alu-PVC / Alu)	30, 40, 50, 60 and 100 tablets
Portugal	Glaxo Wellcome Farmacêutica, Lda. PRT Rua Dr. António Loureiro	Quomem	150 mg	Prolonged release tablets	Oral use	Blister (PA-Alu-PVC /	30, 40, 50, 60 and 100 tablets

Member State	Marketing Authorisation Holder	Invented Name	Strength	Pharmaceutical Form	Route of administration	Packaging	Package size
	Borges, 3, Arquiparque , Miraflores Algés Tel: +351 214 129 500 Fax: +351 214 121 857					Alu)	
Spain	Laboratorios Dr. Esteve S.A. Avda.Virgen De Montserrat, 221 08041Barcelona Tel: +34 93-446-60-00 Fax: +34 93-450-34-52	Quomen	150 mg	Prolonged release tablets	Oral use	Blister (PA-Alu-PVC / Alu)	30 and 60
Spain	Glaxo Wellcome, S.A. Pque.Tecnologico Madrid Severo Ochoa, 2 28760 Tres Cantos Madrid Tel: +34 91-807-03-01 Fax: +34 91-807-03-10	Zyntabac	150 mg	Prolonged release tablets	Oral use	Blister (PA-Alu-PVC / Alu)	30 and 60
Sweden	GlaxoSmithKline AB, PO Box 263, 431 23 Mölndal Tel: 0046 3167 09 00 Fax: 0046 3127 47 45	Zyban	150 mg	Prolonged release tablets	Oral use	Blister (PA-Alu-PVC / Alu)	1x100 tablets (1x30, 1x40, 1x50, 1x60 tablets; not marketed in Sweden)
United Kingdom	Glaxo Wellcome UK Ltd, Stockley Park West, Uxbridge, Middlesex, UB11 1BT Tel: 020 8990 2896 Fax: 020 8990 4385	Zyban	150 mg	Prolonged release tablets	Oral use	Blister (PA-Alu-PVC / Alu)	60 tablets

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LIST OF THE NAMES, PHARMACEUTICAL FORM, STRENGTHS OF THE MEDICINAL PRODUCTS, ROUTE OF ADMINISTRATION, MARKETING AUTHORISATION HOLDERS, PACKAGING AND PACKAGE SIZES IN ICELAND AND NORWAY.

BUPROPION CONTAINING MEDICINAL PRODUCTS WITH MARKETING AUTHORISATION IN ICELAND AND NORWAY

Member State	Marketing Authorisation Holder	Invented Name	Strength	Pharmaceutical Form	Route of administration	Packaging	Package size
Iceland	GlaxoSmithKline ehf	Zyban	150 mg	Prolonged release tablet	Oral use	Blister (PA-Alu-PVC/Alu)	60, 100
Norway	GlaxoSmithKline AS, P.box 4312 Nydalen 0401 Oslo, Norway Tel: +47 22 58 20 00 Fax: +47 22 58 20 05	Zyban	150 mg	Prolonged release tablets	Oral use	Blister (PA-Alu-PVC/Alu)	60, 100

ANNEX II

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR AMENDMENT OF THE SUMMARY OF PRODUCT CHARACTERISTICS PRESENTED BY THE EMEA

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF BUPROPION CONTAINING MEDICINAL PRODUCTS (see Annex I)

Bupropion is a selective inhibitor of the neuronal re-uptake of catecholamines (noradrenaline and dopamine) with minimal effect on the re-uptake of indolamines (serotonin) and no inhibition of monoamine oxidase.

In the EU, bupropion containing medicinal products were authorised as an "aid to smoking-cessation in combination with motivational support in nicotine-dependent patients" through a Mutual Recognition Procedure (MRP) with the Netherlands as Reference Member State (RMS). Since licensing, concerns were raised in relation to the reports of suspected adverse drug reactions (ADRs) received associated with the use of bupropion containing medicinal products, particularly those of seizure and fatalities. Subsequently, amendments to the terms of marketing authorisations have been introduced to maintain a favourable benefit/risk balance, which resulted in changes to the SPC under the MRP.

On 19 February 2002, Germany triggered a referral to the EMEA under Article 36 of Directive 2001/83/EC. Germany requested the CPMP to give an opinion on whether the marketing authorisations of bupropion containing products indicated as "aid to smoking cessation in combination with motivational support in nicotine-dependent patients" should be maintained or changed in the terms of marketing authorisation or withdrawn, based on the reported serious adverse reactions associated with these products, in particular reports of depression, suicidal ideation, suicide, seizures, undesirable cardiovascular effects, and angioedema, which raise potential public health concerns.

EFFICACY

From the data on efficacy, the evidence that short-term treatment with bupropion (7-9 weeks at 300mg/day) significantly increases the percentage of patients who stop smoking in the short-term is consistent across the three pivotal studies (2,290 patients). The long-term benefit beyond 1 year has not yet been well defined, however, the available data indicate that the long term efficacy of bupropion (defined as continuous abstinence over 12 months) is better than that of placebo. Specifically, the 1-year continuous abstinence rates in the two studies conducted by the company were 13% and 23% among patients treated with bupropion (prolonged-release formulation) compared to 10% and 8% among patients treated with placebo. In comparison, the 12-month continuous abstinence rate for nicotine replacement therapy (NRT) was estimated as being 12% in one study. Meta-analyses further indicate that bupropion seems to be slightly superior to treatment with NRT.

Bupropion has been shown to be an effective aid to smoking cessation in a variety of patient groups. Comparable efficacy was demonstrated for patients with previous failed quit attempts and patients without such experience and for patients with and without psychiatric and cardiac morbidity. However, long term efficacy was not demonstrated in patients with chronic obstructive pulmonary disease. Although limited data are available for other sub-populations, the available data do not indicate any specific sub-group for whom there might be reason to suspect lack of efficacy.

Comparison of the efficacy of bupropion observed in routine clinical practice to that in clinical trials suggest also that the level of motivational support provided is not a key factor in determining the efficacy of bupropion.

SAFETY

Pre-clinical findings

Serious neurotoxicity, including convulsions occurs in animals at dose levels giving plasma bupropion and plasma bupropion metabolite levels comparable to human therapeutic plasma levels, especially when these levels are expressed as pharmacodynamic bupropion equivalents. It is evident the preclinical data do not allow for a safety margin with respect to the neurotoxic effects of bupropion.

This lack of a safety margin was already noted during the initial evaluation and at that time it was concluded that the safety of bupropion had to be based mainly on the available clinical data.

The MAHs reviewed the existing preclinical data on the cardiovascular effects of bupropion. The data suggest that bupropion at therapeutic doses does not produce significant effects on ECG parameters.

Since no new preclinical data were submitted, the current overview may be considered on its own merits but does not really add to this risk/benefit assessment.

Clinical findings

The post-marketing experience with bupropion to date does not conclusively support the existence of major unexpected risks. The most commonly reported reactions are non-serious including insomnia, rash, headache and dizziness. The adverse event profile of bupropion is similar to that of NRT, with the notable exceptions of seizures and hypersensitivity, although spontaneous reporting data suggest that bupropion may not be as well tolerated.

Seizures and hypersensitivity (due to frequency of occurrence) are the most important risk. These reactions were recognised at the time of licensing and warnings have been present in the SPC since bupropion was first licensed in the EU. The available data from spontaneous reporting do not suggest that in routine clinical practice these reactions occur more frequently than expected.

Suicidal ideation was seen in 6 subjects out of the total of 4067 (0.15%) exposed to bupropion in the clinical trials. Spontaneous reports of suicidal ideation have also been received in patients treated with bupropion for smoking cessation during the post-marketing period. The rate of suicidal ideation with bupropion is low compared to the rates found in the general population. There is neither a pharmacodynamic nor a clinical reason for suspecting bupropion to be causally associated with depression or suicide.

Furthermore, depressed mood is a recognised symptom of nicotine withdrawal and a smoker's mood typically worsens in the first few days of abstinence. It is difficult to distinguish the reports of depression and suicidal ideation from symptoms of nicotine withdrawal since information on smoking status has been provided in very few reports. Overall the available data are not suggestive of a causal relationship between bupropion and suicidal ideation. Although a warning already exists in Section 4.4 (Warnings and Precautions For Use) about the possibility of severe depression during a smoking cessation attempt with bupropion, the SPC wording has been further strengthened to warn prescribers that these reactions generally occurred early in the course of treatment and patients should be advised accordingly.

The majority of reports of cardiovascular and cerebrovascular disorders occur in individuals with underlying cardiovascular disease or other risk factors in addition to smoking. The possibility that it may be causally associated with certain arrhythmias and cerebrovascular disorders cannot be entirely excluded. It is advised that the existing warnings regarding the risk of hypertension are further strengthened to recommend that consideration is given to stopping treatment in patients who experience a clinically significant rise in blood pressure.

Serious adverse drug reactions occur in association with bupropion. However this risk is present during a fixed period of treatment (normally 7-9 weeks) and should be considered in the context of the long term beneficial effects of smoking cessation including reduction of the risk of strokes and heart disease.

Overall, the above summary of suspected adverse drug reactions observed in association with bupropion indicates that no major new safety issues have emerged during the period since its licensing as an aid for smoking cessation. Furthermore, the adverse drug reaction profile of bupropion does not seem to be a cause for alarm or concern. Although the total number of adverse reactions may seem high, the large number of exposed individuals has to be kept in mind (31.5 million patients exposed for all indications and formulations of bupropion, 9.2 million for smoking cessation only). Therefore, rates rather than absolute numbers should be considered. When this is done, it appears that these rates are broadly consistent with what can reasonably be expected.

The conclusion that is drawn is therefore that the evidence collected from the accumulated ADRs does not call for a change to or the removal of the licence of bupropion in the current indication.

BENEFIT/RISK ANALYSIS

Based on re-evaluation of the currently available information on bupropion, the majority of the CPMP considered that:

- Bupropion has been shown to be an effective aid to smoking cessation;
- The post-marketing experience with bupropion does not support the existence of major unexpected risks;
- The relevant warning in the SPC regarding hypersensitivity, hypertension and depression should be strengthened.
- The risks recognised to occur in association with bupropion should be considered in the context of the beneficial effects of smoking cessation which are potentially more long term;
- Overall the balance of risks and benefits of bupropion remains favourable for the current indication (i.e.: "as an aid to smoking cessation in combination with motivational support in nicotine-dependent patients")
- Considering the above, the restriction of the use of bupropion to a second line treatment or to a special population is not warranted. However, it is recommended that bupropion should be used in accordance with smoking cessation guidelines.

Therefore the CPMP considered that the benefit/risk balance of bupropion containing medicinal products is favourable and the Marketing Authorisations should be maintained according to the Summary of Product Characteristics as set out in Annex III of the CPMP Opinion with emphasis to the following:

Section 4.2 Posology and method of administration – Recommendation to use bupropion in accordance with smoking cessation guidelines. Moreover, prescribers should assess the patient's motivation to quit. Smoking cessation therapies are more likely to succeed in those patients whom are motivated to quit and have motivational support.
As insomnia is a very common adverse event, which can be reduced by avoiding bedtime doses of bupropion (provided there is at least 8 hours between doses).

Section 4.3 Contraindications – The reason for the contraindication in bipolar disorder was added.

Section 4.4 Special warnings and precautions for use – The following neuropsychiatry information is given: Bupropion is a centrally-acting noradrenaline/dopamine reuptake inhibitor and as such the pharmacology resembles that of some antidepressants. Neuropsychiatric reactions have been reported (see 4.8 Undesirable Effects). In particular, psychotic and manic symptomatology have been reported mainly in patients with a known history of psychiatric illness.
The warning on depression is strengthened to warn prescribers that these reactions generally occurred early in the course of treatment and patients should be advised accordingly.
The warning on hypersensitivity is strengthened to stress that bupropion should be discontinued if patients experience hypersensitivity reactions during treatment. Clinicians should be aware that symptoms may progress or recur following the discontinuation of bupropion and should ensure symptomatic treatment is administered for an adequate length of time (at least one week). Symptoms typically include skin rash, pruritus, urticaria or chest pain, but more severe reactions may include angioedema, dyspnoea/bronchospasm, anaphylactic shock, erythema multiforme or Stevens-Johnson Syndrome.
With regards to the warning on hypertension, it is advised that consideration should be given to discontinuation of bupropion if a clinically significant increase in blood pressure is observed.

Section 4.5 Interaction – Information of interaction with alcohol is stressed. Although clinical data do not identify a pharmacokinetic interaction between bupropion and alcohol, there have been rare reports of adverse neuropsychiatric events or reduced alcohol tolerance in patients drinking alcohol during bupropion treatment. The consumption of alcohol during bupropion treatment should be minimised or avoided.

Section 4.8 Undesirable effects – Change in frequency of insomnia from common to very common. Addition of dystonia, ataxia, Parkinsonism, twitching and incoordination.

Section 5.1 – Pharmacotherapeutic group in accordance with WHO classification.

GROUNDS FOR AMENDMENT OF THE SUMMARY OF PRODUCT CHARACTERISTICS

Whereas

- The Committee considered the referral made under article 36 of Directive 2001/83/EC, for bupropion containing medicinal products;

- The Committee agreed that bupropion has been shown to be an effective aid to smoking cessation.

- The Committee agreed that the post-marketing experience with bupropion does not support the existence of major unexpected risks and the risks recognised to occur in association with bupropion should be considered in the context of the beneficial effects of smoking cessation which are potentially more long term.

- The Committee, as a consequence, considered the benefit/risk balance of bupropion containing medicinal products to be favourable as an aid to smoking cessation in combination with motivational support in nicotine-dependent patients, and, therefore, concluded that the Marketing Authorisations for these medicinal products should be maintained in accordance with the Summary of Product Characteristics set out in Annex III.

As a consequence the CPMP has recommended the maintenance of the Marketing Authorisations for bupropion containing medicinal products referred to in Annexes I as amended in accordance with the Summary of Product Characteristics set out in Annex III.

ANNEX III

SUMMARY OF PRODUCT CHARACTERISTICS

Note: This SPC is the one that was annexed to the Commission Decision on this Article 36 referral for bupropion containing medicinal products. The texts were valid at that time.

It is not subsequently maintained or updated by the EMEA, and therefore may not necessarily represent the current texts.

1. NAME OF THE MEDICINAL PRODUCT

<Invented Name> 150 mg prolonged release tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains bupropion as bupropion hydrochloride 150 mg.
For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Prolonged release tablet.
White, film-coated, biconvex, round tablet printed on one side with GX CH7 and plain on the other side.

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

<Invented Name> tablets are indicated as an aid to smoking cessation in combination with motivational support in nicotine-dependent patients.

4.2. Posology and Method of Administration

<Invented Name> should be used in accordance with smoking cessation guidelines.

Prescribers should assess the patient's motivation to quit. Smoking cessation therapies are more likely to succeed in those patients whom are motivated to quit and have motivational support.
<Invented Name> tablets should be swallowed whole and not crushed or chewed.
Patients should be treated for 7-9 weeks.
Although discontinuation reactions are not expected with <Invented Name>, a tapering-off period may be considered.
If at seven weeks no effect is seen, treatment should be discontinued.

Use in Adults
It is recommended that treatment is started while the patient is still smoking and a "target stop date" set within the first two weeks of treatment with <Invented Name>, preferably in the second week.
The initial dose is 150mg to be taken daily for six days, increasing on day seven to 150mg twice daily.
There should be an interval of at least 8 hours between successive doses.
The maximum single dose must not exceed 150mg and the maximum total daily dose must not exceed 300mg.
Insomnia is a very common adverse event which can be reduced by avoiding bedtime doses of <Invented Name> (provided there is at least 8 hours between doses).

Use in Children and Adolescents
Use in patients under 18 years of age is not recommended as the safety and efficacy of <Invented Name> tablets have not been evaluated in these patients.

Use in Elderly Patients
<Invented Name> should be used with caution in elderly patients. Greater sensitivity in some elderly individuals cannot be ruled out. The recommended dose in the elderly is 150mg once a day.

Use in Patients with Hepatic Insufficiency
<Invented Name> should be used with caution in patients with hepatic impairment. Because of increased variability in the pharmacokinetics in patients with mild to moderate impairment the recommended dose in these patients is 150mg once a day.

Use in Patients with Renal Insufficiency
<Invented Name> should be used with caution in patients with renal insufficiency. The recommended dose in these patients is 150mg once a day.

4.3. Contraindications

<Invented Name> is contraindicated in patients with hypersensitivity to bupropion or any of the excipients.
<Invented Name> is contraindicated in patients with a current seizure disorder or any history of seizures.
<Invented Name> is contraindicated in patients with a known central nervous system (CNS) tumour.
<Invented Name> is contraindicated in patients who, at any time during treatment, are undergoing abrupt withdrawal from alcohol or any medicinal product known to be associated with risk of seizures on withdrawal (in particular benzodiazepines and benzodiazepine-like agents).
<Invented Name> is contraindicated in patients with a current or previous diagnosis of bulimia or anorexia nervosa.
<Invented Name> is contraindicated for use in patients with severe hepatic cirrhosis.
Concomitant use of <Invented Name> and monoamine oxidase inhibitors (MAOIs) is contraindicated. At least 14 days should elapse between discontinuation of irreversible MAOIs and initiation of treatment with <Invented Name>. For reversible MAOIs, a 24 hour period is sufficient.
<Invented Name> is contraindicated in patients with a history of bipolar disorder as it may precipitate a manic episode during the depressed phase of their illness.

4.4. Special Warnings and Precautions for Use

Seizures
The recommended dose of <Invented Name> must not be exceeded, since bupropion is associated with a dose-related risk of seizure. At doses up to the maximum recommended daily dose (300mg of <Invented Name> daily), the incidence of seizures is approximately 0.1% (1/1,000).
There is an increased risk of seizures occurring with the use of <Invented Name> in the presence of predisposing risk factors which lower the seizure threshold. <Invented Name> must not be used in patients with predisposing risk factors unless there is a compelling clinical justification for which the potential medical benefit of smoking cessation outweighs the potential increased risk of seizure. In these patients, a maximum dose of 150mg daily should be considered for the duration of treatment.
All patients should be assessed for predisposing risk factors, which include:

- concomitant administration of other medicinal products known to lower the seizure threshold (e.g., antipsychotics, antidepressants, antimalarials, tramadol, theophylline, systemic steroids, quinolones and sedating antihistamines). For patients prescribed such medicinal products whilst taking <Invented Name>, a maximum dose of 150mg daily for the remainder of their treatment should be considered.
- alcohol abuse
- history of head trauma
- diabetes treated with hypoglycaemics or insulin
- use of stimulants or anorectic products.

<Invented Name> should be discontinued and not recommenced in patients who experience a seizure while on treatment.

Interactions (see 4.5 Interaction with other medicinal products and other forms of interaction)
Due to pharmacokinetic interactions plasma levels of bupropion or its metabolites may be altered, which may increase the potential for undesirable effects (e.g. dry mouth, insomnia, seizures). Therefore care should be taken when bupropion is given concomitantly with medicinal products which can induce or inhibit the metabolism of bupropion.
Bupropion inhibits metabolism by cytochrome P450 2D6. Caution is advised when medicinal products metabolised by this enzyme are administered concomitantly.

Neuropsychiatry
<Invented Name> is a centrally-acting noradrenaline/dopamine reuptake inhibitor and as such the pharmacology resembles that of some antidepressants. Neuropsychiatric reactions have been reported (see 4.8 Undesirable Effects). In particular, psychotic and manic symptomatology have been reported mainly in patients with a known history of psychiatric illness.
Depressed mood may be a symptom of nicotine withdrawal. Depression, rarely including suicidal ideation, has been reported in patients undergoing a smoking cessation attempt. These symptoms have also been reported during <Invented Name> treatment, and generally occurred early during the treatment course. Clinicians should be aware of the possible emergence of significant depressive symptomatology in patients undergoing a smoking cessation attempt, and should advise patients accordingly.
Data in animals suggest a potential for drug abuse. However, studies on abuse liability in humans and extensive clinical experience show that bupropion has low abuse potential.

Hypersensitivity
<Invented Name> should be discontinued if patients experience hypersensitivity reactions during treatment. Clinicians should be aware that symptoms may progress or recur following the discontinuation of <Invented Name> and should ensure symptomatic treatment is administered for an adequate length of time (at least one week). Symptoms typically include skin rash, pruritus, urticaria or chest pain, but more severe reactions may include angioedema, dyspnoea/bronchospasm, anaphylactic shock, erythema multiforme or Stevens-Johnson Syndrome. Arthralgia, myalgia and fever have also been reported in association with rash and other symptoms suggestive of delayed hypersensitivity. These symptoms may resemble serum sickness (See 4.8 Undesirable Effects). In most patients symptoms improved after stopping bupropion and initiating treatment with antihistamine or corticosteroids, and resolved over time.

Hypertension
In clinical practice, hypertension, which in some cases may be severe (see 4.8 Undesirable Effects) and require acute treatment, has been reported in patients receiving bupropion alone and in combination with nicotine replacement therapy. This has been observed in patients with and without pre-existing hypertension. A baseline blood pressure should be obtained at the start of treatment with subsequent monitoring, especially in patients with pre-existing hypertension. Consideration should be given to discontinuation of <Invented Name> if a clinically significant increase in blood pressure is observed.
Limited clinical trial data suggest that higher smoking cessation rates may be achieved by the combination use of <Invented Name> together with Nicotine Transdermal System (NTS). However, a higher rate of treatment-emergent hypertension was noted in the combination therapy group. If combination therapy with a NTS is used, caution must be exercised and weekly monitoring of blood pressure is recommended. Prior to initiation of combination therapy prescribers should consult the prescribing information of the relevant NTS.

Specific patient groups
Elderly – Clinical experience with bupropion has not identified any differences in tolerability between elderly and other adult patients. However, greater sensitivity of some elderly individuals cannot be ruled out. Elderly patients are more likely to have decreased renal function, hence 150 mg once a day is the recommended dose in these patients.

Hepatically-impaired - Bupropion is extensively metabolised in the liver to active metabolites, which are further metabolised. No statistically significant differences in the pharmacokinetics of bupropion were observed in patients with mild to moderate hepatic cirrhosis compared with healthy volunteers, but bupropion plasma levels showed a higher variability between individual patients. Therefore <Invented Name> should be used with caution in patients with mild to moderate hepatic impairment and 150 mg once a day is the recommended dose in these patients.
All patients with hepatic impairment should be closely monitored for possible undesirable effects (e.g., insomnia, dry mouth) that could indicate high drug or metabolite levels.
Renally-impaired - Patients with impaired renal function were not studied. Bupropion is mainly excreted into urine as its metabolites. Therefore 150 mg once a day is the recommended dose in patients with renal impairment, as bupropion and its metabolites may accumulate in such patients to a greater extent than usual. The patient should be closely monitored for possible undesirable effects that could indicate high drug or metabolite levels.

4.5. Interaction with other medicinal products and other forms of interaction

In patients receiving medicinal products known to lower the seizure threshold, <Invented Name> must only be used if there is a compelling clinical justification for which the potential medical benefit of smoking cessation outweighs the increased risk of seizure (see 4.4 Special Warnings and Precautions for use).

The effect of bupropion on other medicinal products:
Although not metabolised by the CYP2D6 isoenzyme, bupropion and its main metabolite, hydroxybupropion, inhibit the CYP2D6 pathway. Co-administration of bupropion hydrochloride and desipramine to healthy volunteers known to be extensive metabolisers of the CYP2D6 isoenzyme resulted in large (2- to 5-fold) increases in the C_{max} and AUC of desipramine. Inhibition of CYP2D6 was present for at least 7 days after the last dose of bupropion hydrochloride.
Although not formally studied, concomitant therapy with medicinal products with narrow therapeutic indices that are predominantly metabolised by CYP2D6 should be initiated at the lower end of the dose range of the concomitant medicinal product. Such medicinal products include certain antidepressants (e.g. desipramine, imipramine, paroxetine), antipsychotics (e.g. risperidone, thioridazine), beta-blockers (e.g. metoprolol), and Type 1C antiarrhythmics (e.g. propafanone, flecainide). If <Invented Name> is added to the treatment regimen of a patient already receiving such a medicinal product, the need to decrease the dose of the original medicinal product should be considered. In these cases the expected benefit of treatment with <Invented Name> should be carefully considered compared with the potential risks.

The effect of other medicinal products on bupropion:
In vitro findings indicate that bupropion is metabolised to its major active metabolite hydroxybupropion primarily by the cytochrome P450 CYP2B6 (see 5.2 Pharmacokinetic Properties). Care should therefore be exercised when <Invented Name> is co-administered with medicinal products that may affect the CYP2B6 isoenzyme (e.g.: orphenadrine, cyclophosphamide, ifosfamide). Since bupropion is extensively metabolised, caution is advised when bupropion is co-administered with medicinal products known to induce metabolism (e.g. carbamazepine, phenytoin) or inhibit metabolism (e.g. valproate), as these may affect its clinical efficacy and safety.
Nicotine, administered transdermally by patches, did not affect the pharmacokinetics of bupropion and its metabolites.

Other interactions:
Smoking is associated with an increase in CYP1A2 activity. After cessation of smoking, reduced clearance of medicinal products metabolised by this enzyme, with subsequent increases in plasma levels, may occur. This may be particularly important for those medicinal products primarily metabolised by CYP1A2 with narrow therapeutic windows (e.g. theophylline, tacrine and clozapine).

The clinical consequences of smoking cessation on other medicinal products that are partially metabolised by CYP1A2 (e.g., imipramine, olanzapine, clomipramine, and fluvoxamine) are unknown. In addition, limited data indicate that the metabolism of flecainide or pentazocine may also be induced by smoking.
Administration of <Invented Name> to patients receiving either levodopa or amantadine concurrently should be undertaken with caution. Limited clinical data suggest a higher incidence of undesirable effects (e.g. nausea, vomiting, and neuropsychiatric events – see 4.8 Undesirable Effects) in patients receiving bupropion concurrently with either levodopa or amantadine.
Although clinical data do not identify a pharmacokinetic interaction between bupropion and alcohol, there have been rare reports of adverse neuropsychiatric events or reduced alcohol tolerance in patients drinking alcohol during <Invented Name> treatment. The consumption of alcohol during <Invented Name> treatment should be minimised or avoided.
Since monoamine oxidase A and B inhibitors also enhance the catecholaminergic pathways, by a different mechanism from bupropion, concomitant use of <Invented Name> and monoamine oxidase inhibitors (MAOIs) is contraindicated (see 4.3 Contra-indications) as there is an increased possibility of adverse reactions from their co-administration. At least 14 days should elapse between discontinuation of irreversible MAOIs and initiation of treatment with <Invented Name>. For reversible MAOIs, a 24 hour period is sufficient.

4.6. Pregnancy and lactation

The safety of <Invented Name> for use in human pregnancy has not been established.
Evaluation of experimental animal studies does not indicate direct or indirect harmful effects with respect to the development of the embryo or foetus, the course of gestation and peri-natal or post-natal development. Exposure in animals was, however, similar to the systemic exposure achieved in humans at the maximum recommended dose. The potential risk in humans is unknown.
Pregnant women should be encouraged to quit smoking without the use of pharmacotherapy.
<Invented Name> should not be used in pregnancy.
As bupropion and its metabolites are excreted in human breast milk mothers should be advised not to breast feed while taking <Invented Name>.

4.7. Effects on ability to drive and use machines

As with other CNS acting drugs bupropion may affect ability to perform tasks that require judgement or motor and cognitive skills. <Invented Name> has also been reported to cause dizziness and lightheadedness. Patients should therefore exercise caution before driving or use of machinery until they are reasonably certain <Invented Name> does not adversely affect their performance.

4.8. Undesirable effects

The list below provides information on the undesirable effects identified from clinical experience, categorised by incidence and body system. It is important to note that smoking cessation is often associated with nicotine withdrawal symptoms (e.g. agitation, insomnia, tremor, sweating), some of which are also recognised as adverse events associated with <Invented Name>.
Undesirable effects are ranked under headings of frequency using the following convention; very common (>1/10); common (>1/100, <1/10); uncommon (>1/1,000, <1/100); rare (>1/10000, <1/1,000).

Cardiovascular	Uncommon	Tachycardia, increased blood pressure (sometimes severe), flushing
	Rare	Vasodilation, postural hypotension, syncope
CNS	Very common	Insomnia (see 4.2 Posology and Method of Administration)
	Common	Tremor, concentration disturbance, headache, dizziness, depression (see 4.4 Special Warnings and Precautions for Use), agitation, anxiety
	Uncommon	Confusion
	Rare	Seizures (see below), irritability, hostility, hallucinations, depersonalisation, dystonia, ataxia, Parkinsonism, twitching, incoordination
Endocrine and metabolic	Uncommon	Anorexia.
	Rare	Blood glucose disturbances
Gastrointestinal	Common	Dry mouth, gastrointestinal disturbance including nausea and vomiting, abdominal pain, constipation
General (body)	Common	Fever
	Uncommon	Chest pain, asthenia
Hepatobiliary	Rare	Elevated liver enzymes, jaundice, hepatitis
Skin / Hypersensitivity:	Common	Rash, pruritus, sweating. Hypersensitivity reactions such as urticaria.
	Rare	More severe hypersensitivity reactions including angioedema, dyspnoea/bronchospasm and anaphylactic shock. Arthralgia, myalgia and fever have also been reported in association with rash and other symptoms suggestive of delayed hypersensitivity. These symptoms may resemble serum sickness. Erythema multiforme and Stevens Johnson syndrome have also been reported. Exacerbation of psoriasis
Special senses	Common	Taste disorders
	Uncommon	Tinnitus, visual disturbance

The incidence of seizures is approximately 0.1% (1/1,000). The most common type of seizures is generalised tonic-clonic seizures, a seizure type which can result in some cases in post-ictal confusion or memory impairment. (See 4.4 Special Warnings And Precautions for Use).

4.9. Overdose

Acute ingestion of doses in excess of 10 times the maximum therapeutic dose has been reported. In addition to those events reported as Undesirable Effects, overdose has resulted in symptoms including drowsiness and loss of consciousness. Although most patients recovered without sequelae, deaths associated with overdoses of bupropion have been reported rarely in patients ingesting massive doses of the drug.
Treatment: In the event of overdose, hospitalisation is advised.
Ensure an adequate airway, oxygenation and ventilation. Gastric lavage may be indicated if performed soon after ingestion. The use of activated charcoal is also recommended. No specific antidote for bupropion is known.

5. Pharmacological Properties

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: drugs used in nicotine dependence, ATC code: N07B A02
Bupropion is a selective inhibitor of the neuronal re-uptake of catecholamines (noradrenaline and dopamine) with minimal effect on the re-uptake of indolamines (serotonin) and does not inhibit either monoamine oxidase. The mechanism by which bupropion enhances the ability of patients to abstain from smoking is unknown.
However, it is presumed that this action is mediated by noradrenergic and/or dopaminergic mechanisms.

5.2. Pharmacokinetic properties

Absorption
After oral administration of 150 mg bupropion hydrochloride as a prolonged release tablet to healthy volunteers, maximum plasma concentrations (C_{max}) of approximately 100 nanograms per ml are observed after about 2.5 to 3 hours. The AUC and C_{max} values of bupropion and its active metabolites hydroxybupropion and threohydrobupropion increase dose proportionally over a dose range of 50-200 mg following single dosing and over a dose range of 300-450 mg/day following chronic dosing. The C_{max} and AUC values of hydroxybupropion are approximately 3 and 14 times higher, respectively, than bupropion C_{max} and AUC values. The C_{max} of threohydrobupropion is comparable with the C_{max} of bupropion, while the AUC of threohydrobupropion is approximately 5 times higher than that of bupropion. Peak plasma levels of hydroxybupropion and threohydrobupropion are reached after about 6 hours following administration of a single dose of bupropion. Plasma levels of erythrohydrobupropion (an isomer of threohydrobupropion, which is also active) are not quantifiable after single dosing with bupropion.
After chronic dosing with bupropion 150 mg bid, the C_{max} of bupropion is similar to values reported after single dosing. For hydroxybupropion and threohydrobupropion, the C_{max} values are higher (about 4 and 7 times respectively) at steady-state than after a single dosing. Plasma levels of erythrohydrobupropion are comparable to steady-state plasma levels of bupropion. Steady-state of bupropion and its metabolites is reached within 5-8 days. The absolute bioavailability of bupropion is not known; excretion data in urine, however, show that at least 87% of the dose of bupropion is absorbed. The absorption of bupropion is not significantly influenced when taken concurrently with food.

Distribution
Bupropion is widely distributed with an apparent volume of distribution of approximately 2000 L. Bupropion, hydroxybupropion and threohydrobupropion bind moderately to plasma proteins (84%, 77% and 42%, respectively).
Bupropion and its active metabolites are excreted in human breast milk. Animal studies show that bupropion and its active metabolites pass the blood-brain barrier and the placenta.

Metabolism
Bupropion is extensively metabolised in humans. Three pharmacologically active metabolites have been identified in plasma: hydroxybupropion and the amino-alcohol isomers, threohydrobupropion and erythrohydrobupropion. These may have clinical importance, as their plasma concentrations are as high or higher than those of bupropion. The active metabolites are further metabolised to inactive metabolites (some of which have not been fully characterised but may include conjugates) and excreted in the urine.
In vitro studies indicate that bupropion is metabolised to its major active metabolite hydroxybupropion primarily by the CYP2B6, while CYP1A2, 2A6, 2C9, 3A4 and 2E1 are less involved. In contrast, formation of threohydrobupropion involves carbonyl reduction but does not involve cytochrome P450 isoenzymes. (See 4.5 Interaction with Other Medicinal Products and Other Forms of Interaction)
The inhibition potential of threohydrobupropion and erythrohydrobupropion towards cytochrome P450 has not been studied.
Bupropion and hydroxybupropion are both inhibitors of the CYP2D6 isoenzyme with K_i values of 21 and 13.3µM, respectively (See 4.5 Interaction with Other Medicinal Products and Other Forms of Interaction).
Following oral administration of a single 150-mg dose of bupropion, there was no difference in C_{max}, half-life, T_{max}, AUC, or clearance of bupropion or its major metabolites between smokers and non-smokers.
Bupropion has been shown to induce its own metabolism in animals following sub-chronic administration. In humans, there is no evidence of enzyme induction of bupropion or hydroxybupropion in volunteers or patients receiving recommended doses of bupropion hydrochloride for 10 to 45 days.

Elimination

Following oral administration of 200mg of ^{14}C-bupropion in humans, 87% and 10% of the radioactive dose were recovered in the urine and faeces, respectively. The fraction of the dose of bupropion excreted unchanged was only 0.5%, a finding consistent with the extensive metabolism of bupropion. Less than 10% of this ^{14}C dose was accounted for in the urine as active metabolites.
The mean apparent clearance following oral administration of bupropion hydrochloride is approximately 200 L/hr and the mean elimination half-life of bupropion is approximately 20 hours. The elimination half-life of hydroxybupropion is approximately 20 hours. The elimination half-lives for threohydrobupropion and erythrohydrobupropion are longer (37 and 33 hours, respectively).

<u>Special Patient Groups</u>:

Patients with renal impairment
The effect of renal disease on the pharmacokinetics of bupropion has not been studied. The elimination of the major metabolites of bupropion may be affected by reduced renal function. (See 4.4 Special Warnings and Precautions for Use).

Patients with hepatic impairment
The pharmacokinetics of bupropion and its active metabolites were not statistically significantly different in patients with mild to moderate cirrhosis when compared to healthy volunteers, although more variability was observed between individual patients. (see 4.4 Special Warnings And Precautions for Use)

For patients with severe hepatic cirrhosis, the bupropion Cmax and AUC were substantially increased (mean difference approximately 70% and 3-fold, respectively) and more variable when compared to the values in healthy volunteers; the mean half-life was also longer (by approximately 40%). For hydroxybupropion, the mean Cmax was lower (by approximately 70%), the mean AUC tended to be higher (by approximately 30%), the median Tmax was later (by approximately 20 hrs), and the mean half-lives were longer (by approximately 4-fold) than in healthy volunteers. For threohydrobupropion and erythrohydrobupropion, the mean Cmax tended to be lower (by approximately 30%), the mean AUC tended to be higher (by approximately 50%), the median Tmax was later (by approximately 20 hrs), and the mean half-life was longer (by approximately 2-fold) than in healthy volunteers. (see 4.3 Contraindications)

Elderly patients
Pharmacokinetic studies in the elderly have shown variable results. A single dose study showed that the pharmacokinetics of bupropion and its metabolites in the elderly do not differ from those in the younger adults. Another pharmacokinetic study, single and multiple dose, has suggested that accumulation of bupropion and its metabolites may occur to a greater extent in the elderly. Clinical experience has not identified differences in tolerability between elderly and younger patients, but greater sensitivity in older patients cannot be ruled out. (see 4.4 Special Warnings And Precautions for Use)

5.3. Preclinical Safety Data

In animal experiments bupropion doses several times higher than therapeutic doses in humans caused, amongst others, the following dose-related symptoms: ataxia and convulsions in rats, general weakness, trembling and emesis in dogs and increased lethality in both species. Due to enzyme induction in animals but not in humans, systemic exposures in animals were similar to the systemic exposures seen in humans at the maximum recommended dose.
Liver changes are seen in animal studies but these reflect the action of a hepatic enzyme inducer. At recommended doses in humans, bupropion does not induce its own metabolism. This suggests that the hepatic findings in laboratory animals have only limited importance in the evaluation and risk assessment of bupropion.
Genotoxicity data indicate that bupropion is a weak bacterial mutagen, but not a mammalian mutagen, and therefore is of no concern as a human genotoxic agent. Mouse and rat studies confirm the absence of carcinogenicity in these species.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Tablet core
Microcrystalline cellulose
Hypromellose
Cysteine hydrochloride monohydrate
Magnesium stearate

Film coat
Hypromellose
Macrogol 400
Titanium dioxide (E171)
Carnauba wax (as polish)

Printing ink
Iron oxide black (E172)
Hypromellose

6.2. Incompatibilities

Not applicable

6.3. Shelf Life

2 years.

6.4. Special precautions for storage

Do not store above 25°C. Store in the original package.

6.5. Nature and contents of container

Cartons containing cold form foil / foil blister packs (PA-Alu-PVC / Alu).
30, 40, 50, 60 or 100 tablets are supplied in each pack. Each blister strip contains 10 tablets. Not all pack sizes may be marketed.

6.6. Instructions for use and handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

To be completed as appropriate.

8. MARKETING AUTHORISATION NUMBER

To be completed as appropriate.

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

To be completed as appropriate.

10. DATE OF (PARTIAL) REVISION OF THE TEXT

