2. Sa DS, *et al.* Amoxapine shows an antipsychotic effect but worsens motor function in patients with Parkinson's disease and psychosis. *Clin Neuropharmacol* 2001; **24:** 242–4.
3. Apiquian R, *et al.* Amoxapine shows atypical antipsychotic effects in patients with schizophrenia: results from a prospective open-label study. *Schizophr Res* 2003; **59:** 35–9.
4. Fitzgerald PB, *et al.* Amoxapine in schizophrenia: a negative double-blind controlled trial. *J Clin Psychopharmacol* 2004; **24:** 448–50.
5. Apiquian R, *et al.* Amoxapine as an atypical antipsychotic: a comparative study vs risperidone. *Neuropsychopharmacology* 2005; **30:** 2236–44.

Preparations

USP 31: Amoxapine Tablets.

Proprietary Preparations (details are given in Part 3)
Denm.: Demolox†; ***Fr.:*** Defanyl; ***India:*** Demolox; ***Indon.:*** Asendin; ***UK:*** Asendis†; ***USA:*** Asendin†.

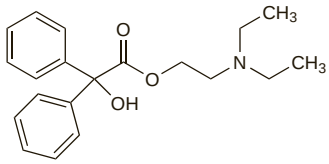
Benactyzine Hydrochloride *(BANM, rINNM)*

Amizylum; Bénactyzine, Chlorhydrate de; Benactyzini Hydrochloridum; Hidrocloruro de benacticina. 2-Diethylaminoethyl benzilate hydrochloride.

Бенактизина Гидрохлорид

$C_{20}H_{25}NO_3$,HCl = 363.9.

CAS — 302-40-9 (benactyzine); 57-37-4 (benactyzine hydrochloride).



(benactyzine)

Profile

Benactyzine has antidepressant and antimuscarinic activity. It has been used as the hydrochloride in the management of depression and associated anxiety. It is also used as a pharmacological tool. Methylbenactyzium bromide (p.1747), the methobromide of benactyzine, has been used for its antimuscarinic activity in the treatment of gastrointestinal spasm and nocturnal enuresis.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: *Arg.:* Dimaval.

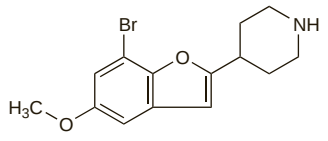
Brofaromine *(rINN)*

Brofaromina; Brofarominum; CGP-11305A (brofaromine hydrochloride). 4-(7-Bromo-5-methoxy-2-benzofuranyl)piperidine.

Брофаромин

$C_{14}H_{16}BrNO_2$ = 310.2.

CAS — 63638-91-5.



Profile

Brofaromine is a reversible inhibitor of monoamine oxidase type A (RIMA) (see Moclobemide, p.411). It has been studied in the treatment of depression and in anxiety disorders including social anxiety disorder.

Bupropion Hydrochloride

(BANM, USAN, rINNM)

Amfebutamone Hydrochloride; Bupropione, Chlorhydrate de; Bupropionhydroklorid; Bupropioni Hydrochloridum; Bupropionihydrokloridi; BW-323; Hidrocloruro de bupropión. (±)-2-(*tert*-Butylamino)-3′-chloropropiophenone hydrochloride.

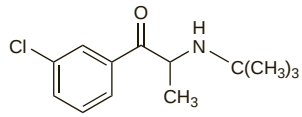
Бупропиона Гидрохлорид

$C_{13}H_{18}ClNO$,HCl = 276.2.

CAS — 34911-55-2 (bupropion); 31677-93-7 (bupropion hydrochloride).

ATC — N07BA02.

ATC Vet — QN07BA02.



(bupropion)

Pharmacopoeias. In *US.*
USP 31 (Bupropion Hydrochloride). A white powder. Soluble in water, in alcohol, and in 0.1N hydrochloric acid. Protect from light.

Adverse Effects and Treatment

Agitation, anxiety, and insomnia often occur during the initial stages of bupropion therapy. Other relatively common adverse effects reported with bupropion include fever, dry mouth, headache or migraine, dizziness, urinary frequency, nausea and vomiting, constipation, tremor, sweating, and skin rashes. Hypersensitivity reactions, ranging from pruritus and urticaria to, less commonly, angioedema, dyspnoea, and anaphylactoid reactions, have occurred, as have symptoms suggestive of serum sickness. There have been rare reports of Stevens-Johnson syndrome and erythema multiforme. Tachycardia, chest pain, and hypertension (sometimes severe), or occasionally vasodilatation, orthostatic hypotension, palpitations, and syncope have been reported. Psychotic episodes, confusion, nightmares, impaired memory, dysgeusia, anorexia with weight loss, paraesthesia, tinnitus, and visual disturbances have also been reported.

Hyponatraemia, possibly due to inappropriate secretion of antidiuretic hormone, has been associated with the use of antidepressants, particularly in the elderly.

Seizures, which appear to be partially dose-related, may occur with bupropion and have been particularly notable in patients with anorexia nervosa or bulimia nervosa; the risk is also increased in patients with a history of seizure disorders or other predisposing factor. The manufacturers state that the overall incidence of seizure in patients receiving bupropion at recommended doses is about 0.1 to 0.4%.

Symptoms of overdosage include hallucinations, nausea and vomiting, tachycardia, loss of consciousness, and death (following massive overdose); seizures have occurred in about one-third of all bupropion overdose cases. Activated charcoal should be considered in adult patients who have taken more than 450 mg and in all children, if they present within 1 hour of ingestion; gastric lavage may also be used to decrease absorption. Treatment is supportive. Benzodiazepines may be tried for seizures. Diuresis, dialysis, and haemoperfusion are unlikely to be of benefit.

Incidence of adverse effects. Up to 24 July 2002 (the first 25 months of marketing), the UK CSM had received 7630 reports of suspected adverse reactions associated with the use of bupropion.[1] Of these reports, 60 were associated with a fatal outcome although in most cases underlying conditions could have been responsible. Cardiovascular and cerebrovascular disorders such as myocardial infarction and stroke were reported as the cause of death in 70% of cases. The CSM also commented that adverse reactions were mainly recognised ones and listed in the licensed product information.

In January 2005 the German pharmacovigilance network reviewed[2] 273 reports of adverse effects associated with bupropion, received between June 2000 and September 2004. The most frequent adverse effects were: psychiatric disorders (79.3%), including suicide attempts (17.6%), and tachycardia (11.15%), seizures (8.8%), and dyspnoea (8.8%). There were also 4 cases of pancreatitis and one of raised pancreatic enzyme activity three times greater than normal.

1. CSM/MCA. Zyban (bupropion hydrochloride) - safety update (issued 26th July 2002). Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON019524&RevisionSelectionMethod=LatestReleased (accessed 08/06/06)
2. Drug Commission of the German Medical Association. Increased pancreatic enzymes or acute pancreatitis induced by bupropion (Zyban)(from the UAW database). Available at: http://www.akdae.de/en/20/20/Archiv/2005/800_20050110.html (accessed 04/06/06)

Effects on the cardiovascular system. Up to the end of December 2001 the national pharmacovigilance centre in the Netherlands had received 591 adverse reaction reports associated with the use of bupropion for smoking cessation since its marketing 2 years earlier;[1] of these, 45 concerned cardiac complaints such as palpitations (21), arrhythmias (7), myocardial infarction (3), anginal pain (2), and cardiac arrest (1). Twenty-two reports also mentioned chest pain or tightness, although these were considered to be of noncardiac origin. In another report a 43-year-old male suffered an acute myocardial infarction 2 weeks after starting bupropion for smoking cessation;[2] he had experienced central chest and arm pain 3 days before the infarction. The authors of the report said that up to 30 April 2001 the UK CSM had received 238 reports of chest pain and 134 reports of chest tightness associated with bupropion use.

1. de Graaf L, Diemont WL. Chest pain during use of bupropion as an aid in smoking cessation. *Br J Clin Pharmacol* 2003; **56:** 451–2.
2. Patterson RN, Herity NA. Acute myocardial infarction following bupropion (Zyban). *QJM* 2002; **95:** 58–9.

Effects on the cerebrovascular system. A 67-year-old male had paraesthesia, dizziness, tinnitus, confusion, and gait impairment after taking bupropion for smoking cessation.[1] Although a transient ischaemic attack was suspected symptoms resolved on stopping bupropion and recurred on rechallenge.

1. Humma LM, Swims MP. Bupropion mimics a transient ischemic attack. *Ann Pharmacother* 1999; **33:** 305–7.

Effects on the pancreas. See under Incidence of Adverse Effects, above.

Effects on the skin. *Erythema multiforme* developed in a 31-year-old woman several weeks after starting modified-release bupropion for depression.[1] Symptoms resolved on drug withdrawal. In another report, 3 patients with controlled *psoriasis* had an exacerbation of their psoriatic symptoms after starting bupropion for smoking cessation.[2] All 3 patients required hospitalisation to control their symptoms. There have also been several reports of patients developing *generalised acute urticaria*;[3,4] systemic symptoms resembling serum sickness were also reported in 1 case[4] (see also Hypersensitivity, below).

1. Lineberry TW, *et al.* Bupropion-induced erythema multiforme. *Mayo Clin Proc* 2001; **76:** 664–6.
2. Cox NH, *et al.* Generalized pustular and erythrodermic psoriasis associated with bupropion treatment. *Br J Dermatol* 2002; **146:** 1061–3.
3. Fays S, *et al.* Bupropion and generalized acute urticaria: eight cases. *Br J Dermatol* 2003; **148:** 177–8.
4. Loo WJ, *et al.* Bupropion and generalized acute urticaria: a further case. *Br J Dermatol* 2003; **149:** 660.

Extrapyramidal effects. A 44-year-old man had acute head and neck dystonia while taking buspirone and modified-release bupropion.[1] No recurrence was noted on rechallenge with buspirone although symptoms did develop on rechallenge with bupropion when the dose was increased from 150 mg once daily to 150 mg twice daily. In another case, a 42-year-old woman had gross involuntary movements of her torso, arms, and legs (diagnosed as ballism) 8 days after starting bupropion for smoking cessation;[2] the dose had been increased from 150 mg once daily to 150 mg twice daily on the fourth day. She recovered when bupropion was stopped and treatment with haloperidol and oxazepam was given.

1. Detweiler MB, Harpold GJ. Bupropion-induced acute dystonia. *Ann Pharmacother* 2002; **36:** 251–4.
2. de Graaf L, *et al.* Ballism associated with bupropion use. *Ann Pharmacother* 2003; **37:** 302–3.

Hypersensitivity. Eosinophilia has been reported[1] in a patient 12 days after bupropion was added to her existing treatment regimen of glibenclamide and tolmetin. The eosinophil count returned to normal after all medication was stopped. Bupropion appeared to be the causative drug.

Serum sickness or symptoms suggestive of serum sickness has also been associated with bupropion use.[2-5] In one case,[5] although the initial presentation resembled serum sickness, the patient went on to develop multisystem complications that included hepatitis, cholestasis, and myocarditis.

See also Effects on the Skin, above.

1. Malesker MA, *et al.* Eosinophilia associated with bupropion. *Ann Pharmacother* 1995; **29:** 867–8.
2. Yolles JC, *et al.* Serum sickness induced by bupropion. *Ann Pharmacother* 1999; **33:** 931–3.
3. McCollom RA, *et al.* Bupropion-induced serum sickness-like reaction. *Ann Pharmacother* 2000; **34:** 471–3.
4. Benson E. Bupropion-induced hypersensitivity reactions. *Med J Aust* 2001; **174:** 650–1.
5. Bagshaw SM, *et al.* Drug-induced rash with eosinophilia and systemic symptoms syndrome with bupropion administration. *Ann Allergy Asthma Immunol* 2003; **90:** 572–5.

Overdosage. Unlike the tricyclic antidepressants, bupropion appears to lack any significant cardiovascular or antimuscarinic adverse effects when taken in overdose. In an early review[1] of 58 overdose cases involving immediate-release bupropion alone, the most common symptoms were sinus tachycardia, lethargy, tremor, and seizures; other effects included confusion, lightheadedness, hallucinations, paraesthesias, and vomiting. Most patients had minor effects or none at all. Similar symptoms have also been noted in reviews of overdose cases involving modified-release bupropion.[2,3] UK licensed prescribing information for bupropion also lists ECG changes such as conduction disturbances, arrhythmias, and tachycardia although a literature review[4] concluded that cardiotoxicity appeared to be rare with

bupropion overdosage. Although rare, there have been fatalities after overdose; in some cases other drugs may have been involved.[3,5,6]

More recent case reports and reviews with modified-release preparations have highlighted that seizures are a particular feature of bupropion overdose.[2,3,7,8]

1. Spiller HA, *et al.* Bupropion overdose: a 3-year multi-center retrospective analysis. *Am J Emerg Med* 1994; **12:** 43–5.
2. Balit CR, *et al.* Bupropion poisoning: a case series. *Med J Aust* 2003; **178:** 61–3.
3. Shepherd G, *et al.* Intentional bupropion overdoses. *J Emerg Med* 2004; **27:** 147–51.
4. Druteika D, Zed PJ. Cardiotoxicity following bupropion overdose. *Ann Pharmacother* 2002; **36:** 1791–5.
5. Friel PN, *et al.* Three fatal drug overdoses involving bupropion. *J Anal Toxicol* 1993; **17:** 436–8.
6. Harris CR, *et al.* Fatal bupropion overdose. *J Toxicol Clin Toxicol* 1997; **35:** 321–4.
7. Bhattacharjee C, *et al.* Bupropion overdose: a potential problem with the new 'miracle' anti-smoking drug. *Int J Clin Pract* 2001; **55:** 221–2.
8. Paoloni R, Szekely I. Sustained-release bupropion overdose: a new entity for Australian emergency departments. *Emerg Med (Fremantle)* 2002; **14:** 109–12.

Precautions

Bupropion may induce seizures and consequently its use is contra-indicated in patients with epilepsy. It is also contra-indicated in patients with a history of anorexia nervosa or bulimia nervosa, as a higher incidence of seizures has been noted in such patients treated with bupropion, and in those undergoing abrupt withdrawal from alcohol or benzodiazepines. It should be used with extreme caution, if at all, in patients with a history of seizure disorders or other predisposing factors such as severe hepatic cirrhosis or a CNS tumour. The use of bupropion in patients with other risk factors for seizures (for example, alcohol abuse, a history of head trauma, diabetes, and drugs known to lower the seizure threshold) should only be undertaken when there are compelling clinical reasons.

Bupropion should be used with caution in patients with bipolar disorder or psychoses because of the risk of precipitating mania; use for smoking cessation in such patients may be contra-indicated. It should also be used cautiously in patients with a recent history of myocardial infarction or unstable heart disease, and in hepatic or renal impairment.

When bupropion is used for depression, patients should be closely monitored during early therapy until significant improvement is observed because suicide is an inherent risk in depressed patients. For further details, see under Depression, p.373. Suicidal thoughts and behaviour may also develop during early treatment with antidepressants for other disorders; the same precautions observed when treating patients with depression should therefore be observed when treating patients with other disorders.

As with other CNS-active drugs, the ability to perform tasks requiring motor or cognitive skills or judgement may be impaired by bupropion, and patients, if affected, should not drive or operate machinery.

Breast feeding. The American Academy of Pediatrics considers[1] that the effect of bupropion on nursing infants is unknown but may be of concern.

There has been a report of accumulation of bupropion in human breast milk in concentrations higher than those in maternal plasma.[2] However, neither bupropion nor its metabolites were detected in the plasma of the infant who was breast fed twice daily by the affected mother, and no adverse effects were noted in the infant. Similar findings have been noted in a more recent study in 2 breast-fed infants whose mothers took bupropion for postpartum depression.[3] However, in another report, a 6-month-old infant had a seizure after being fed breast milk that had been expressed and stored 2 days earlier, after the infant's mother had taken a single dose of bupropion.[4] Before the seizure, the mother had taken 2 doses of bupropion and breast fed the infant several times with no adverse effects.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 24/11/05)
2. Briggs GC, *et al.* Excretion of bupropion in breast milk. *Ann Pharmacother* 1993; **27:** 431–3.
3. Baab SW, *et al.* Serum bupropion levels in 2 breastfeeding mother-infant pairs. *J Clin Psychiatry* 2002; **63:** 910–11.
4. Chaudron LH, Schoenecker CJ. Bupropion and breastfeeding: a case of a possible infant seizure. *J Clin Psychiatry* 2004; **65:** 881–2.

Children. Bupropion has not been studied for the treatment of depression in adolescents and children; consequently its use in patients under 18 years of age, regardless of indication, is not recommended. In addition, other antidepressants have been shown to increase the risk of suicidal thoughts and behaviour in these patients (see Effects on Mental State, under Fluoxetine, p.392).

Pregnancy. The safety of bupropion in pregnancy has not been established. In a study of 136 women who took bupropion for either depression or smoking cessation in at least the first trimester of pregnancy, there were 105 live births, 20 spontaneous abortions, 10 therapeutic abortions, 1 still-birth, and 1 neonatal death; no major congenital malformations were reported.[1] Compared to a control group not exposed to teratogens, the rate of spontaneous abortions was significantly higher in the bupropion group when both indications were considered; however, there was no difference in the rate when women taking bupropion for depression were compared to this control group and another control group of women taking other antidepressants.

Complications at birth requiring prolonged hospitalisation, breathing support, and tube feeding have been reported with some of the newer antidepressants such as bupropion.[2] Other reported symptoms have included seizures, muscle rigidity, jitteriness, and prolonged crying. It is not known whether such symptoms represent a direct toxicity of bupropion or a possible withdrawal syndrome.

1. Chun-Fai-Chan B, *et al.* Pregnancy outcome of women exposed to bupropion during pregnancy: a prospective comparative study. *Am J Obstet Gynecol* 2005; **192:** 932–6.
2. Health Canada. Health Canada advises of potential adverse effects of SSRIs and other anti-depressants on newborns (issued 9th August 2004). Available at: http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2004/2004_44-eng.php (accessed 14/08/08)

Interactions

Bupropion should not be given with or within 14 days of stopping an MAOI; however, no treatment-free period is necessary after stopping a reversible inhibitor of monoamine oxidase type A (RIMA) and starting bupropion.

The use of alcohol with bupropion should be minimised or avoided completely because it may alter the seizure threshold. Similarly, extreme caution is needed if other drugs that lower the seizure threshold, such as other antidepressants, antimalarials, antipsychotics, sedating antihistamines, quinolones, tramadol, theophylline, or systemic corticosteroids are used with bupropion. In the UK, where it is licensed as a modified-release product for smoking cessation, a maximum dose of 150 mg daily is recommended if patients are also taking such drugs.

Use of nicotine transdermal patches with bupropion has been associated with hypertension, and patients using both should therefore have their blood pressure monitored.

Caution has been advised in patients receiving either amantadine or levodopa with bupropion because of reports of a higher incidence of adverse effects in patients receiving these combinations.

Animal studies have indicated that bupropion may induce drug-metabolising enzymes and pharmacokinetic interactions with other drugs are therefore a possibility. Bupropion is itself metabolised by hepatic enzyme systems and drugs known to affect such systems may interact with bupropion. For example carbamazepine, phenobarbital, or phenytoin may induce the metabolism of bupropion while other drugs such as cimetidine or valproate may inhibit its metabolism. *In-vitro* studies have shown that bupropion is metabolised by the cytochrome P450 isoenzyme CYP2B6. Consequently interactions may occur between bupropion and drugs that affect this isoenzyme, for example orphenadrine, cyclophosphamide, and ifosfamide.

In-vitro studies have also shown that bupropion is also an inhibitor of the isoenzyme CYP2D6; caution should be exercised when it is given with drugs metabolised by this isoenzyme and they should be started at the lower end of their dose range. Such drugs include some antidepressants, antipsychotics, beta blockers, and type Ic antiarrhythmics.

Antiepileptics. Plasma-bupropion concentrations became undetectable in 2 patients who were also receiving *carbamazepine*; plasma concentrations of hydroxybupropion, an active metabolite of bupropion, were high.[1]

1. Popli AP, *et al.* Bupropion and anticonvulsant drug interactions. *Ann Clin Psychiatry* 1995; **7:** 99–101.

Antivirals. There is some evidence from study *in vitro* that the antivirals *efavirenz*, *nelfinavir*, and *ritonavir* can inhibit the cytochrome P450 isoenzyme CYP2B6,[1] and licensed product information for ritonavir mentions the possibility of an interaction with bupropion. However, evidence of clinically significant interaction is lacking: a small case series of 10 patients who took bupropion with low-dose ritonavir (100 mg twice daily), or efavirenz or nelfinavir, did not note any episodes of seizures.[2] A study[3] in 7 healthy male subjects also found that 2 days of low-dose ritonavir (200 mg twice daily) had little impact on the pharmacokinetics of a single bupropion dose.

In contrast, the UK licensed product information for bupropion describes a study in healthy subjects in which 20 days of full-dose ritonavir (600 mg twice daily) reduced the area under the concentration-time curve (AUC) and maximum plasma concentration of bupropion, possibly by inducing its metabolism. Plasma concentrations of bupropion's active metabolites were also reduced. In another study[4] in healthy subjects, the plasma concentrations and AUC of bupropion and its active metabolite hydroxybupropion, from a single dose of bupropion, were reduced by about 50% after 14 days of a *lopinavir/ritonavir* combination (400 mg/100 mg twice daily). This effect was attributed to induction of CYP2B6 and UDP-glucuronosyltransferase by the HIV-protease inhibitor combination. In discussing the contrasting results that have been reported, the authors suggested that the higher ritonavir concentrations achieved *in-vitro* had an inhibitory effect, compared with the inducing effect of lower steady-state concentrations achieved *in-vivo*.

1. Hesse LM, *et al.* Ritonavir, efavirenz, and nelfinavir inhibit CYP2B6 activity in vitro: potential drug interactions with bupropion. *Drug Metab Dispos* 2001; **29:** 100–102.
2. Park-Wyllie LY, Antoniou T. Concurrent use of bupropion with CYP2B6 inhibitors, nelfinavir, ritonavir and efavirenz: a case series. *AIDS* 2003; **17:** 638–40.
3. Hesse LM, *et al.* Ritonavir has minimal impact on the pharmacokinetic disposition of a single dose of bupropion administered to human volunteers. *J Clin Pharmacol* 2006; **46:** 567–76.
4. Hogeland GW, *et al.* Lopinavir/ritonavir reduces bupropion plasma concentrations in healthy subjects. *Clin Pharmacol Ther* 2007; **81:** 69–75.

Histamine H_2-antagonists. A randomised controlled study in 24 subjects found that *cimetidine* had no effect on the pharmacokinetics of modified-release bupropion or its active metabolite, hydroxybupropion.[1]

1. Kustra R, *et al.* Lack of effect of cimetidine on the pharmacokinetics of sustained-release bupropion. *J Clin Pharmacol* 1999: **39:** 1184–8.

Pharmacokinetics

Bupropion is well absorbed from the gastrointestinal tract but may undergo extensive first-pass metabolism. Several metabolites of bupropion are pharmacologically active and have longer half-lives, and achieve higher plasma concentrations, than the parent compound. Hydroxybupropion is the major metabolite, produced by the metabolism of bupropion by the cytochrome P450 isoenzyme CYP2B6; in *animal* studies hydroxybupropion was one-half as potent as bupropion. Threohydrobupropion and erythrohydrobupropion are produced by reduction and are about one-fifth the potency of the parent compound. Bupropion is 80% or more bound to plasma proteins. The terminal plasma half-life of immediate-release bupropion is about 14 hours; the terminal plasma half-life of modified-release bupropion is about 20 hours. The metabolites of bupropion are excreted primarily in the urine; less than 1% of the parent drug is excreted unchanged. Bupropion and its metabolites cross the placenta and are distributed into breast milk.

◊ References.

1. Sweet RA, *et al.* Pharmacokinetics of single- and multiple-dose bupropion in elderly patients with depression. *J Clin Pharmacol* 1995; **35:** 876–84.

Smoking. No clinically significant differences were seen between the pharmacokinetics of bupropion or its metabolites in cigarette smokers and non-smokers.[1]

1. Hsyu P-H, *et al.* Pharmacokinetics of bupropion and its metabolites in cigarette smokers versus nonsmokers. *J Clin Pharmacol* 1997; **37:** 737–43.

Uses and Administration

Bupropion is a chlorpropiophenone antidepressant chemically unrelated to other classes of antidepressants but similar in structure to the central stimulant diethylpropion (p.2154). It is a weak blocker of neuronal reuptake of serotonin and noradrenaline compared

with tricyclic antidepressants; it also inhibits the neuronal reuptake of dopamine. The antidepressant effect may not be evident until after 4 weeks of therapy. Bupropion is also used as an aid to smoking cessation.

Bupropion is given orally as the hydrochloride. To minimise agitation, anxiety, and insomnia often experienced at the start of therapy, and to reduce the risk of seizures, doses should be increased gradually; the total daily dose should be given in equally divided doses and the maximum recommended single and total daily doses should not be exceeded. Insomnia at the start of therapy may be minimised by avoiding bedtime doses. Patients with hepatic or renal impairment should be given reduced doses and monitored for toxic effects (see below).

In the treatment of **depression** bupropion hydrochloride is given in initial doses of 100 mg twice daily increased, if necessary, after at least 3 days to 100 mg three times daily. In severe cases, if no improvement has been observed after several weeks of therapy, the dose may be increased further to a maximum of 150 mg three times daily. Bupropion hydrochloride is also available as a modified-release preparation given in an initial dose of 150 mg once daily in the morning increased, if necessary, after at least 3 days to 150 mg twice daily; in severe cases, the dose of the modified-release preparation may be increased further after several weeks to 200 mg twice daily. A modified-release preparation that is given once daily is also available; the maximum daily dose for this preparation is 450 mg as a single dose in the morning. A modified-release preparation is also licensed for the prevention of depression in patients with seasonal affective disorder; the maximum dose for this disorder is 300 mg once daily.

Bupropion hydrochloride is given as a modified-release preparation as an aid to **smoking cessation** in an initial dose of 150 mg once daily for 6 days, increasing to 150 mg twice daily on day 7. In the USA, the dose may be increased after 3 days. In the UK, the maximum recommended dose in the elderly, or in patients with predisposing risk factors for seizure (see Precautions, above), is 150 mg daily. Treatment should be started about 1 to 2 weeks before the patient attempts to stop smoking, to allow steady-state blood levels of bupropion to be reached, and normally continues for 7 to 12 weeks; if there is no significant progress towards smoking abstinence by the seventh week, then therapy should be stopped. Use with nicotine transdermal patches may be warranted in some patients, although there is a risk of hypertension with such therapy (see Interactions, above).

Administration in hepatic impairment. When used as an aid to *smoking cessation* in patients with mild to moderate hepatic impairment, bupropion should be given at a reduced frequency; UK licensed product information suggests an oral dose of 150 mg once daily. The use of bupropion in patients with severe hepatic cirrhosis is contra-indicated in the UK although doses of 150 mg every other day are permitted in the USA.

In the treatment of *depression*, a reduction in the frequency and/or the dose of bupropion should be considered in patients with mild to moderate impairment. In patients with severe hepatic cirrhosis the dose varies according to the preparation given; for modified-release bupropion the suggested maximum oral dose is 100 mg once daily or 150 mg every other day while the maximum dose of immediate-release bupropion is 75 mg once daily.

Administration in renal impairment. When used as an aid to *smoking cessation* in patients with renal impairment, bupropion should be given at a reduced frequency; UK licensed product information suggests an oral dose of 150 mg once daily.

In the treatment of *depression*, a reduction in the frequency and/or the dose of bupropion should be considered.

Depression. As discussed on p.373, there is very little difference in efficacy between the different groups of antidepressant drugs, and choice is often made on the basis of adverse effect profile. Bupropion has a different biochemical profile from both the tricyclics and the SSRIs; however, like the SSRIs, it may be safer in overdosage than the older tricyclics.

References.
1. Kavoussi RJ, *et al.* Double-blind comparison of bupropion sustained release and sertraline in depressed outpatients. *J Clin Psychiatry* 1997; **58:** 532–7.
2. Nieuwstraten CE, Dolovich LR. Bupropion versus selective serotonin-reuptake inhibitors for treatment of depression. *Ann Pharmacother* 2001; **35:** 1608–13.
3. Weihs KL, *et al.* Continuation phase treatment with bupropion SR effectively decreases the risk for relapse of depression. *Biol Psychiatry* 2002; **51:** 753–61.
4. Glod CA, *et al.* Open trial of bupropion SR in adolescent major depression. *J Child Adolesc Psychiatr Nurs* 2003; **16:** 123–30.
5. Rush AJ, *et al.* The STAR*D Study Team. Bupropion-SR, sertraline, or venlafaxine-XR after failure of SSRIs for depression. *N Engl J Med* 2006; **354:** 1231–42.
6. Papakostas GI, *et al.* Comparing the rapidity of response during treatment of major depressive disorder with bupropion and the SSRIs: a pooled survival analysis of 7 double-blind, randomized clinical trials. *J Clin Psychiatry* 2007; **68:** 1907–12.
7. Dhillon S, *et al.* Bupropion: a review of its use in the management of major depressive disorder. *Drugs* 2008; **68:** 653–89.

Hyperactivity. When drug therapy is indicated for attention deficit hyperactivity disorder (p.2148) initial treatment is usually with a central stimulant. Antidepressants may be used for patients who fail to respond to, or who are intolerant of, central stimulants. Data from open and controlled studies involving small numbers of patients suggest that bupropion is effective in adults and children.[1,2]

1. Cantwell DP. ADHD through the life span: the role of bupropion in treatment. *J Clin Psychiatry* 1998; **59** (suppl 4): 92–4.
2. Wilens TE, *et al.* A controlled clinical trial of bupropion for attention deficit hyperactivity disorder in adults. *Am J Psychiatry* 2001; **158:** 282–8.

Smoking cessation. Bupropion is effective in the management of smoking cessation (p.2354) and may be used as a first-line alternative to nicotine replacement therapy (NRT); its action is said to be independent of its antidepressant activity. Bupropion with NRT has also been used successfully although there is an increased risk of hypertension with this combination (see Interactions, above).

References:
1. Hurt RD, *et al.* A comparison of sustained-release bupropion and placebo for smoking cessation. *N Engl J Med* 1997; **337:** 1195–1202.
2. Jorenby DE, *et al.* A controlled trial of sustained-release bupropion, a nicotine patch, or both for smoking cessation. *N Engl J Med* 1999; **340:** 685–91.
3. Holm KJ, Spencer CM. Bupropion: a review of its use in the management of smoking cessation. *Drugs* 2000; **59:** 1007–1024.
4. Tashkin DP, *et al.* Smoking cessation in patients with chronic obstructive pulmonary disease: a double-blind, placebo-controlled, randomised trial. *Lancet* 2001; **357:** 1571–5.
5. Gonzales DH, *et al.* Bupropion SR as an aid to smoking cessation in smokers treated previously with bupropion: a randomized placebo-controlled study. *Clin Pharmacol Ther* 2001; **69:** 438–44.
6. Hays JT, *et al.* Sustained-release bupropion for pharmacologic relapse prevention after smoking cessation: a randomized, controlled trial. *Ann Intern Med* 2001; **135:** 423–33.
7. NICE. Guidance on the use of nicotine replacement therapy (NRT) and bupropion for smoking cessation: Technology Appraisal 39 (issued March 2002). Available at: http://www.nice.org.uk/nicemedia/pdf/NiceNRT39GUIDANCE.pdf (accessed 14/08/08)
8. Ahluwalia JS, *et al.* Sustained-release bupropion for smoking cessation in African Americans: a randomized controlled trial. *JAMA* 2002; **288:** 468–74.
9. Fagerström K, *et al.* Smoking cessation treatment with sustained-release bupropion: optimising approaches to management. A seminar-in-print. *Drugs* 2002; **62** (suppl 2): 1–70.
10. Hays JT, Ebbert JO. Bupropion sustained release for treatment of tobacco dependence. *Mayo Clin Proc* 2003; **78:** 1020–4.
11. Tonnesen P, *et al.* A multicentre, randomized, double-blind, placebo-controlled, 1-year study of bupropion SR for smoking cessation. *J Intern Med* 2003; **254:** 184–92.
12. Simon JA, *et al.* Bupropion for smoking cessation: a randomized trial. *Arch Intern Med* 2004; **164:** 1797–1803.
13. Hatsukami DK, *et al.* Effects of sustained-release bupropion among persons interested in reducing but not quitting smoking. *Am J Med* 2004; **116:** 151–7.
14. Roddy E. ABC of smoking cessation: bupropion and other non-nicotine pharmacotherapies. *BMJ* 2004; **328:** 509–11.
15. Hughes JR, *et al.* Antidepressants for smoking cessation. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 14/08/08).
16. Paluck EC, *et al.* Outcomes of bupropion therapy for smoking cessation during routine clinical use. *Ann Pharmacother* 2006; **40:** 185–90.

Preparations

USP 31: Bupropion Hydrochloride Extended-Release Tablets; Bupropion Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Odranal; Wellbutrin; ***Austral.:*** Clorpax; Prexaton; Zyban; ***Austria:*** Quomem; Zyban; ***Belg.:*** Zyban; ***Braz.:*** Bup; Wellbutrin; Zetron; Zyban; ***Canad.:*** Wellbutrin; Zyban; ***Chile:*** Buxon; Dosier†; Mondrian†; Wellbutrin; ***Cz.:*** Elontril; Wellbutrin; Zyban; ***Denm.:*** Zyban; ***Fin.:*** Zyban; ***Fr.:*** Zyban; ***Ger.:*** Zyban; ***Gr.:*** Zyban; ***Hong Kong:*** Wellbutrin; Zyban; ***Hung.:*** Wellbutrin; Zyban†; ***India:*** Nicotex; Zyban; ***Irl.:*** Zyban; ***Israel:*** Zyban; ***Ital.:*** Quomem†; Zyban; ***Malaysia:*** Zyban; ***Mex.:*** Butrew; Wellbutrin; ***Neth.:*** Quomem; Zyban; Zyntabac; ***Norw.:*** Zyban; ***NZ:*** Zyban; ***Pol.:*** Zyban; ***Port.:*** Elontril; Wellbutrin; Zyban; Zyntabac; ***S.Afr.:*** Wellbutrin; Zyban; ***Singapore:*** Wellbutrin; Zyban; ***Spain:*** Quomem; Zyntabac; ***Swed.:*** Zyban; ***Switz.:*** Zyban; ***Thai.:*** Quomem; ***Turk.:*** Zyban; ***UK:*** Zyban; ***USA:*** Budeprion; Wellbutrin; Zyban; ***Venez.:*** Wellbutrin; Zyban†.

Citalopram *(BAN, rINN)*

Citalopramum; Lu-10-171; Sitalopraami. 1-(3-Dimethylaminopropyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile.

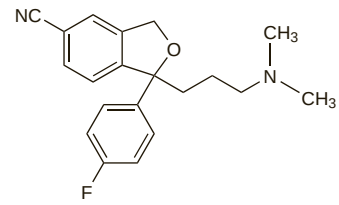
Циталопрам

$C_{20}H_{21}FN_2O$ = 324.4.

CAS — 59729-33-8.

ATC — N06AB04.

ATC Vet — QN06AB04.



Citalopram Hydrobromide *(BANM, USAN, rINNM)*

Citalopram, bromhydrate de; Citaloprami hydrobromidum; Hidrobromuro de citalopram; Lu-10-171B; Nitalapram Hydrobromide; Sitalopram Hidrobromür.

Циталопрама Гидробромид

$C_{20}H_{21}FN_2O,HBr$ = 405.3.

CAS — 59729-32-7.

Pharmacopoeias. In *US.*
USP 31 (Citalopram Hydrobromide). A white to almost white, crystalline powder. Freely soluble in water, in alcohol, and in chloroform. A 0.5% solution in water has a pH of 5.5 to 6.5.

Citalopram Hydrochloride *(BANM, rINNM)*

Citalopram, chlorhydrate de; Citaloprami hydrochloridum; Hidrocloruro de citalopram.

Циталопрама Гидрохлорид

$C_{20}H_{21}FN_2O,HCl$ = 360.9.

Adverse Effects, Treatment, and Precautions

As for SSRIs in general (see Fluoxetine, p.391) although increased appetite and weight gain have also been reported with citalopram. Citalopram may be more cardiotoxic in overdosage than other SSRIs; for further details, see p.394.

Breast feeding. For comments on the use of SSRIs in breast feeding patients, see under Precautions for Fluoxetine, p.394.

Children. SSRIs are associated with an increased risk of potentially suicidal behaviour when used for the treatment of depression in children and adolescents under 18 years old; for further details, see under Effects on Mental State in Fluoxetine, p.392.

Interactions

For interactions associated with SSRIs, see Fluoxetine, p.396.

Pharmacokinetics

Citalopram is readily absorbed from the gastrointestinal tract and maximum plasma concentrations are reached 2 to 4 hours after oral doses. Citalopram is widely distributed throughout the body; protein binding is less than 80%. Citalopram is metabolised by demethylation, deamination, and oxidation to active and inactive metabolites. The demethylation of citalopram to one of its active metabolites, demethylcitalopram, involves the cytochrome P450 isoenzymes CYP3A4 and CYP2C19; the metabolism of citalopram is also partly dependent on CYP2D6. Didemethylcitalopram has also been identified as a metabolite of citalopram. The elimination half-life of citalopram is reported to be about 36 hours. It is excreted mainly via the liver (85%) with the remainder via the kidneys. About 12% of the daily dose is excreted in the urine as unchanged drug. Citalopram is distributed into breast milk in very low concentrations (see Breast Feeding under Precautions in Fluoxetine, p.394).