Apomorphine is extensively metabolised in the liver, primarily by conjugation with glucuronic acid or sulfate; the major metabolite is apomorphine sulfate. It is also demethylated to produce norapomorphine. Most of a dose is excreted in urine, mainly as metabolites.

◊ References.

1. Neef C, van Laar T. Pharmacokinetic-pharmacodynamic relationships of apomorphine in patients with Parkinson's disease. *Clin Pharmacokinet* 1999; **37:** 257–71.
2. Argiolas A, Hedlund H. The pharmacology and clinical pharmacokinetics of apomorphine SL. *BJU Int* 2001; **88** (suppl 3): 18–21.
3. LeWitt PA. Subcutaneously administered apomorphine: pharmacokinetics and metabolism. *Neurology* 2004; **62** (suppl 4): S8–S11.

Uses and Administration

Apomorphine is a morphine derivative with structural similarities to dopamine. It is a potent dopamine D_1- and D_2-receptor agonist used in the management of parkinsonism, especially in the control of the 'on-off' effect. It has also been used in the management of erectile dysfunction. Apomorphine is given as the hydrochloride and doses are expressed in terms of this salt. The regimen for parkinsonism given below applies to the UK preparation and doses are give subcutaneously; a similar preparation is available in the USA although the licensed maximum single and daily doses are less than those in the UK.

The optimal dose of apomorphine in the management of 'off' periods in **parkinsonism** should be established individually under specialist care. At least 2 days of pretreatment with the antiemetic domperidone is advised before starting apomorphine. After withholding antiparkinsonian therapy overnight to provoke an 'off' period, a test dose of 1 mg is given initially, followed by a second dose of 2 mg after 30 minutes, if necessary. Subsequent incremental increases should then be given at intervals of at least 40 minutes, as necessary, to determine the lowest dose producing a satisfactory motor response. Once the patient's normal antiparkinsonian therapy is re-established, the effective dose of apomorphine hydrochloride is given at the first signs of an 'off' period.

The dose and frequency are further adjusted according to response; patients typically require 3 to 30 mg daily in divided doses but individual injections should not be greater than 10 mg. Patients who require more than 10 injections daily or those whose overall control of symptoms remains unsatisfactory with intermittent injections may benefit from continuous subcutaneous infusion. The infusion is started at a rate of 1 mg/hour and this may be increased in steps of up to 0.5 mg/hour at intervals of not less than 4 hours to a maximum rate of 4 mg/hour. It is advised that infusions should only be given during waking hours and that the infusion site should be changed every 12 hours; 24-hour infusions are not advised unless there are severe night-time symptoms. Patients usually need to supplement the infusion with intermittent bolus injections but the recommended maximum total daily dose given by infusion and/or injection is 100 mg.

In the management of **erectile dysfunction** the usual initial dose has been 2 mg taken sublingually about 20 minutes before sexual activity. A dose of 3 mg was used on subsequent occasions if necessary with a minimum of 8 hours between doses. Reduced dosage is needed in patients with renal impairment (see below).

Apomorphine stimulates the chemoreceptor trigger zone in the brain and can produce emesis within a few minutes of a dose. However, the use of apomorphine for the induction of emesis in poisoning is considered dangerous owing to the risk of inducing protracted vomiting and shock, and is not recommended.

Administration in renal impairment. In the management of erectile dysfunction, the maximum dose of apomorphine hydrochloride has been limited to 2 mg sublingually in patients with severe renal impairment.

Erectile dysfunction. Apomorphine is among a wide range of drugs that has been used in the management of erectile dysfunction[1-5] (p.2179) with some beneficial results. It is usually given sublingually although it has also been given subcutaneously.[3] Inhaled apomorphine is also under investigation.

1. Heaton JPW, *et al.* Recovery of erectile function by the oral administration of apomorphine. *Urology* 1995; **45:** 200–6.
2. Dula E, *et al.* Efficacy and safety of fixed-dose and dose-optimization regimens of sublingual apomorphine versus placebo in men with erectile dysfunction. *Urology* 2000; **56:** 130–5.
3. Segraves RT, *et al.* Effect of apomorphine on penile tumescence in men with psychogenic impotence. *J Urol (Baltimore)* 1991; **145:** 1174–5.
4. Martinez R, *et al.* Clinical experience with apomorphine hydrochloride: the first 107 patients. *J Urol (Baltimore)* 2003; **170:** 2352–5.
5. Gontero P, *et al.* Clinical efficacy of apomorphine SL in erectile dysfunction of diabetic men. *Int J Impot Res* 2005; **17:** 80–5.

DIAGNOSIS. Test doses of subcutaneous apomorphine have been used in the differential diagnosis of parkinsonian syndromes,[1-4] to distinguish forms responsive to dopaminergics from other parkinsonian syndromes such as Wilson's disease, corticobasal degeneration, and diffuse Lewy-body dementia. Oral challenge with levodopa is still the best test of dopaminergic responsiveness[5,6] but apomorphine has proved of value in re-assessing patients who have become less responsive to levodopa.[1,4]

1. Barker R, *et al.* Subcutaneous apomorphine as a diagnostic test for dopaminergic responsiveness in parkinsonian syndromes. *Lancet* 1989; **i:** 675.
2. Oertel WH, *et al.* Apomorphine test for dopaminergic responsiveness. *Lancet* 1989; **i:** 1262–3.
3. Frankel JP, *et al.* Use of apomorphine to test for dopamine responsiveness in Wilson's disease. *Lancet* 1989; **ii:** 801–2.
4. Hughes AJ, *et al.* Apomorphine test to predict dopaminergic responsiveness in parkinsonian syndromes. *Lancet* 1990; **336:** 32–4.
5. Steiger MJ, Quinn NP. Levodopa challenge test in Parkinson's disease. *Lancet* 1992; **339:** 751–2.
6. Müller T, *et al.* Repeated rating improves value of diagnostic dopaminergic challenge tests in Parkinson's disease. *J Neural Transm* 2003; **110:** 603–9.

Parkinsonism. ***TREATMENT.*** Although apomorphine has produced benefit in Parkinson's disease (p.791) when given orally, the high doses required to overcome extensive first-pass hepatic metabolism (up to 1.4 g daily in one study[1]), were associated with uraemia. The use of apomorphine in Parkinson's disease has therefore been limited by the need for parenteral dosage. The current main use of apomorphine in Parkinson's disease is for the stabilisation of patients with 'on-off' fluctuations unresponsive to other dopamine agonists. It is usually given subcutaneously either by injection or infusion but a review[2] of the use of apomorphine in Parkinson's disease also discussed studies of rectal, sublingual, and intranasal use. Inhaled apomorphine is also under investigation.

1. Cotzias GC, *et al.* Treatment of Parkinson's disease with aporphines. *N Engl J Med* 1976; **294:** 567–72.
2. Koller W, Stacy M. Other formulations and future considerations for apomorphine for subcutaneous injection therapy. *Neurology* 2004; **62** (suppl 4): S22–S26.

Preparations

USP 31: Apomorphine Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Apokinon†; Uprima†; ***Austral.:*** Apomine; ***Austria:*** APO-go; Ixense†; Uprima†; ***Belg.:*** Uprima†; ***Braz.:*** Uprima; ***Chile:*** Noc; Uprima†; ***Cz.:*** APO-go; Uprima†; ***Denm.:*** Uprima†; ***Fin.:*** Uprima†; ***Fr.:*** Apokinon†; Ixense†; Uprima†; ***Ger.:*** APO-go; Ixense†; Uprima†; ***Gr.:*** APO-go; Taluvian†; Uprima†; ***Hong Kong:*** Uprima†; ***Hung.:*** APO-go†; Uprima†; ***Irl.:*** Uprima†; ***Israel:*** APO-go; ***Ital.:*** Apofin; Ixense†; Taluvian†; Uprima†; ***Jpn:*** Ixense; ***Mex.:*** Taluvian; ***Neth.:*** APO-go; Uprima†; ***Norw.:*** Uprima†; ***NZ:*** Apomine; Uprima†; ***Port.:*** APO-go; Uprima†; ***S.Afr.:*** Uprima†; ***Spain:*** APO-go; Taluvian†; Uprima†; ***Swed.:*** Uprima†; ***Switz.:*** Uprima†; ***Thai.:*** Ixense†; ***Turk.:*** APO-go; ***UK:*** APO-go; Uprima†; ***USA:*** Apokyn; ***Venez.:*** Uprima†.

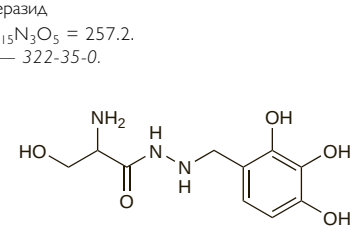
Benserazide *(BAN, USAN, rINN)*

Benseratsidi; Benserazid; Benserazida; Bensérazide; Benserazidum; Ro-4-4602. DL-Serine 2-(2,3,4-trihydroxybenzyl)hydrazide; 2-Amino-3-hydroxy-2'-(2,3,4-trihydroxybenzyl)propionohydrazide.

Бенсеразид

$C_{10}H_{15}N_3O_5$ = 257.2.

CAS — 322-35-0.



Benserazide Hydrochloride *(BANM, rINNM)*

Benseratsidihydrokloridi; Bensérazide, chlorhydrate de; Benserazid-hydrochlorid; Benserazidhydroklorid; Benserazidi hydrochloridum; Benserazido hidrochloridas; Benszerazid-hidroklorid; Hidrocloruro de benserazida; Serazide Hydrochloride.

Бенсеразида Гидрохлорид

$C_{10}H_{15}N_3O_5$,HCl = 293.7.

CAS — 14919-77-8; 14046-64-1.

NOTE. Compounded preparations of benserazide hydrochloride may be represented by the following names:

- Co-beneldopa *(BAN)*—benserazide 1 part and levodopa 4 parts (w/w).

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *Jpn.*

Ph. Eur. 6.2 (Benserazide Hydrochloride). A white or yellowish-white or orange-white crystalline powder. It shows polymorphism. Freely soluble in water; very slightly soluble in dehydrated alcohol; practically insoluble in acetone. A 1% solution in water has a pH of 4.0 to 5.0. Protect from light.

Solubility. Benserazide is unstable in a neutral, alkaline, or strongly acidic medium.[1]

1. Schwartz DE, Brandt R. Pharmacokinetic and metabolic studies of the decarboxylase inhibitor benserazide in animals and man. *Arzneimittelforschung* 1978; **28:** 302–7.

Adverse Effects and Precautions

◊ Early reports[1] noted developmental abnormalities of the *rat* skeleton, but others found no evidence of any disorder involving bone metabolism in man.[2] Nevertheless licensed product information recommends that benserazide should not be given to patients under 25 years of age, nor to pregnant women or to women of child-bearing potential in the absence of adequate contraception.

1. Theiss E, Schärer K. Toxicity of L-dopa and a decarboxylase inhibitor in animal experiments. In: de Ajuriaguerra J, Gauthier G, eds. *Monoamines Noyaux Gris Centraux et Syndrome de Parkinson*. Geneva: Georg, 1971: 497–504.
2. Ziegler WH, *et al.* Toxicity of L-dopa and a dopa decarboxylase inhibitor in humans. In: de Ajuriaguerra J, Gauthier G, eds. *Monoamines Noyaux Gris Centraux et Syndrome de Parkinson*. Geneva: Georg, 1971: 505–16.

Pharmacokinetics

◊ Pharmacokinetic and metabolic studies[1,2] in *animals* and man have shown that, after oral doses in parkinsonian patients, benserazide was rapidly absorbed to the extent of about 58%; giving it with levodopa tended to increase this slightly. Benserazide was rapidly excreted in the urine in the form of metabolites, mostly within the first 6 hours; 85% of urinary excretion had occurred within 12 hours. It is mainly metabolised in the gut and appears to protect levodopa against decarboxylation primarily in the gut, but also in the rest of the organism, mainly by way of its metabolite trihydroxybenzylhydrazine. Benserazide did not cross the blood-brain barrier in *rats*.

1. Schwartz DE, *et al.* Pharmacokinetics of the decarboxylase benserazide in man: its tissue distribution in the rat. *Eur J Clin Pharmacol* 1974; **7:** 39–45.
2. Schwartz DE, Brandt R. Pharmacokinetic and metabolic studies of the decarboxylase inhibitor benserazide in animals and man. *Arzneimittelforschung* 1978; **28:** 302–7.

Uses and Administration

Benserazide hydrochloride is a peripheral dopa-decarboxylase inhibitor with actions similar to those of carbidopa (p.803) and is used similarly as an adjunct to levodopa in the treatment of parkinsonism (p.791). For details of dosage, see Levodopa, p.808.

◊ References.

1. Dingemanse J, *et al.* Pharmacodynamics of benserazide assessed by its effects on endogenous and exogenous levodopa pharmacokinetics. *Br J Clin Pharmacol* 1997; **44:** 41–8.

Preparations

BP 2008: Co-beneldopa Capsules; Dispersible Co-beneldopa Tablets.

Proprietary Preparations (details are given in Part 3)

Ger.: Restex.

Multi-ingredient: ***Arg.:*** Madopar; ***Austral.:*** Madopar; ***Austria:*** Dopamed; Levobens; Madopar; Restex; ***Belg.:*** Prolopa; ***Braz.:*** Prolopa; ***Canad.:*** Prolopa; ***Chile:*** Melitase; Prolopa; ***Cz.:*** Madopar; ***Denm.:*** Madopar; ***Fin.:*** Madopar; ***Fr.:*** Modopar; ***Ger.:*** Levodopa comp B; Levopar; Madopar; PK-Levo; ***Gr.:*** Madopar; ***Hong Kong:*** Madopar; ***Hung.:*** Madopar; ***Indon.:*** Leparson; Levazide; Levopar; Madopar; Pardoz; ***Irl.:*** Madopar; ***Israel:*** Levopar Plus; ***Ital.:*** Madopar; ***Malaysia:*** Madopar; ***Mex.:*** Madopar; ***Neth.:*** Madopar; Modopar; ***Norw.:*** Madopar; ***NZ:*** Madopar; ***Philipp.:*** Madopar; ***Pol.:*** Madopar; ***Port.:*** Madopar; ***Rus.:*** Madopar (Мадопар); ***S.Afr.:*** Madopar; ***Singapore:*** Madopar; ***Spain:*** Madopar; ***Swed.:*** Madopark; ***Switz.:*** Madopar; ***Thai.:*** Cenparkin†; Madopar; Vopar; ***Turk.:*** Madopar; ***UK:*** Madopar; ***Venez.:*** Madopar.