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23. Ekbom K, *et al.* Subcutaneous sumatriptan in the acute treatment of cluster headache: a dose comparison study. *Acta Neurol Scand* 1993; **88:** 63–9.
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26. Monstad I, *et al.* Preemptive oral treatment with sumatriptan during a cluster period. *Headache* 1995; **35:** 607–13.
27. Bahra A, *et al.* Oral zolmitriptan is effective in the acute treatment of cluster headache. *Neurology* 2000; **54:** 1832–39.

Preparations

BP 2008: Sumatriptan Injection; Sumatriptan Nasal Spray; Sumatriptan Tablets;
USP 31: Sumatriptan Nasal Spray; Sumatriptan Succinate Oral Suspension.

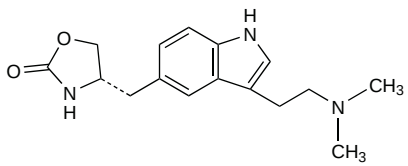
Proprietary Preparations (details are given in Part 3)
Arg.: Imigran; Imitrex†; Micranil; Migraneitor; ***Austral.:*** Imigran; Sumatab; Suvalan; ***Austria:*** Glaxotriptan; Imigran; ***Belg.:*** Imitrex; ***Braz.:*** Imigran; Sumax; ***Canad.:*** Imitrex; ***Chile:*** Imigran; Liotrex†; Somatran; ***Cz.:*** Cinie; Dolorstad; Imigran; Rosemig; Sumamigren; Sumigra; ***Denm.:*** Imigran; ***Fin.:*** Imigran; ***Fr.:*** Imigrane; Imiject; ***Ger.:*** Imigran; ***Gr.:*** Imigran; Sutriptan; ***Hong Kong:*** Imigran; ***Hung.:*** Cinie; Illument; Imigran; ***India:*** Suminat; ***Indon.:*** Cetatrex; Imitrex; Triptagic; ***Irl.:*** Imigran; ***Israel:*** Imitrex; ***Ital.:*** Imigran; Sumigrene†; ***Malaysia:*** Imigran; ***Mex.:*** Imigran; Sumitrex; Tebegran; ***Neth.:*** Imigran; ***Norw.:*** Imigran; ***NZ:*** Imigran; Sumagran; ***Philipp.:*** Imigran; ***Pol.:*** Cinie; Imigran; Sumamigren; Sumigra; ***Port.:*** Diletan†; Imigran; ***Rus.:*** Amigrenin (Амигренин); Imigran (Имигран); ***S.Afr.:*** Imigran; ***Singapore:*** Imigran; ***Spain:*** Arcoiran; Dolmigral†; Imigran; ***Swed.:*** Imigran; ***Switz.:*** Imigran; ***Thai.:*** Imigran; ***Turk.:*** Imigran; Sumatran; ***UK:*** Imigran; ***USA:*** Imitrex; ***Venez.:*** Imigran; Migraval.

Zolmitriptan *(BAN, USAN, rINN)*

311C90; Tsolmitriptaani; Zolmitriptán; Zolmitriptanum. (*S*)-4-{3-[2-(Dimethylamino)ethyl]indol-5-ylmethyl}-1,3-oxazolidin-2-one.

Золмитриптан

$C_{16}H_{21}N_3O_2$ = 287.4.
CAS — 139264-17-8.
ATC — N02CC03.
ATC Vet — QN02CC03.



Adverse Effects and Precautions

As for Sumatriptan, p.625.

Zolmitriptan should also be avoided in patients with Wolff-Parkinson-White syndrome or arrhythmias associated with accessory cardiac conduction pathways. It should be given with caution in patients with moderate to severe hepatic impairment.

Ischaemia. A spinal cord lesion related to the use of zolmitriptan has been reported in a 50-year-old woman;[1] clinical features suggested that the lesion was an ischaemic infarct.

1. Vijayan N, Peacock JH. Spinal cord infarction during use of zolmitriptan: a case report. *Headache* 2000; **40:** 57–60.

Medication-overuse headache. For a report of an association between zolmitriptan and medication-overuse headache, see under Adverse Effects of Sumatriptan, p.626.

Interactions

As for Sumatriptan, p.626.

It is recommended that the maximum dose of zolmitriptan in 24 hours should be reduced in patients receiving cimetidine (see Uses and Administration, below). A similar reduction in zolmitriptan dosage is anticipated if it is given with drugs, such as fluvoxamine and ciprofloxacin, that inhibit the cytochrome P450 isoenzyme CYP1A2. Opinion varies on the use of zolmitriptan with inhibitors of monoamine oxidase type A such as moclobemide. In the UK licensed product information recommends that the maximum dose of zolmitriptan should be reduced when used with inhibitors of monoamine oxidase type A (see Uses and Administration, below), whereas in the USA such combinations are contra-indicated.

◊ References.

1. Dixon R, *et al.* The metabolism of zolmitriptan: effects of an inducer and an inhibitor of cytochrome P450 on its pharmacokinetics in healthy volunteers. *Clin Drug Invest* 1998; **15:** 515–22.

Beta blockers. *Propranolol* increased plasma-zolmitriptan concentrations in a study in 12 healthy subjects, but the changes were not thought to be clinically important enough to warrant dosage adjustment during concomitant use.[1]

1. Peck RW, *et al.* The interaction between propranolol and the novel antimigraine agent zolmitriptan (311C90). *Br J Clin Pharmacol* 1997; **44:** 595–9.

Pharmacokinetics

The absolute bioavailability of zolmitriptan after oral and intranasal doses is about 40%, and peak plasma concentrations are achieved in about 1.5 to 3 hours after oral doses, depending on the formulation, and in about 3 hours with the intranasal spray. Plasma protein binding is about 25%. Zolmitriptan undergoes hepatic metabolism, principally to the indole acetic acid, and also the *N*-oxide and *N*-desmethyl analogues. The *N*-desmethyl metabolite (183C91) was more active than the parent compound in *animal* studies, and would be expected to contribute to the therapeutic effect of zolmitriptan. The primary metabolism of zolmitriptan is mediated mainly by the cytochrome P450 isoenzyme CYP1A2 while monoamine oxidase type A is responsible for further metabolism of the *N*-desmethyl metabolite. Over 60% of a dose is excreted in the urine, mainly as the indole acetic acid, and about 30% appears in the faeces, mainly as unchanged drug. The elimination half-life is 2.5 to 3 hours, and is prolonged in patients with liver disease.

Distribution into milk has been found in studies in *rats*.

◊ References.

1. Dixon R, *et al.* The pharmacokinetics and effects on blood pressure of multiple doses of the novel anti-migraine drug zolmitriptan (311C90) in healthy volunteers. *Br J Clin Pharmacol* 1997; **43:** 273–81.
2. Seaber E, *et al.* The absolute bioavailability and metabolic disposition of the novel antimigraine compound zolmitriptan (311C90). *Br J Clin Pharmacol* 1997; **43:** 579–87.
3. Peck RW, *et al.* The pharmacodynamics and pharmacokinetics of the 5HT -agonist zolmitriptan in healthy young and elderly men and women. *Clin Pharmacol Ther* 1998; **63:** 342–53.
4. Dixon R, *et al.* A comparison of the pharmacokinetics and tolerability of the novel antimigraine compound zolmitriptan in adolescents and adults. *J Child Adolesc Psychopharmacol* 1999; **9:** 35–42.
5. Yates R, *et al.* Pharmacokinetics, dose proportionality, and tolerability of single and repeat doses of a nasal spray formulation of zolmitriptan in healthy volunteers. *J Clin Pharmacol* 2002; **42:** 1244–50.

Uses and Administration

Zolmitriptan is a selective serotonin ($5\text{-}HT_1$) agonist with actions and uses similar to those of sumatriptan (p.627). It is used for the acute treatment of migraine attacks. Zolmitriptan should not be used for prophylaxis.

The recommended dose in the UK is 2.5 mg orally. A clinical response can be expected within 1 hour. If symptoms persist or return within 24 hours, a second dose may be taken not less than 2 hours after the first dose. If a patient does not achieve satisfactory relief with a dose of 2.5 mg, subsequent attacks may be treated with doses of 5 mg. The maximum dose of zolmitriptan in 24 hours is 10 mg. Recommended doses in the USA are somewhat lower; the dose is 1.25 or 2.5 mg with a maximum dose of 10 mg in 24 hours.

When used intranasally a clinical response can be expected in 15 minutes. The usual dose is 5 mg as a single dose into one nostril. If symptoms persist or return within 24 hours, a second dose may be given after at least 2 hours, up to a maximum of 10 mg daily.

Dose reductions are recommended in patients taking certain other drugs. The maximum dose of zolmitriptan in 24 hours should be 5 mg in those receiving cimetidine or an inhibitor of monoamine oxidase type A (although use with inhibitors of monoamine oxidase type A is contra-indicated in the USA). A similar reduction is also recommended in those taking drugs, such as fluvoxamine and ciprofloxacin, that inhibit the cytochrome P450 isoenzyme CYP1A2.

For dosage in hepatic or renal impairment see below.

Administration in hepatic impairment. A study[1] has indicated that while there is no need to reduce the size of the initial dose of zolmitriptan in patients with moderate or severe hepatic impairment, accumulation may occur with repeated doses in patients with severe impairment and their total daily dosage should be reduced.

A maximum oral dose of 5 mg in 24 hours is recommended by licensed product information in the UK in patients with moderate to severe impairment. A dose of less than 2.5 mg is recommended in the USA.

1. Dixon R, *et al.* Effect of hepatic impairment on the pharmacokinetics of zolmitriptan. *J Clin Pharmacol* 1998; **38:** 694–701.

Administration in renal impairment. Although renal clearance of zolmitriptan and its metabolites was reduced in patients with moderate to severe impairment,[1] the resulting effect was unlikely to be of clinical importance and adjustment of zolmitriptan dosage in patients with renal impairment was considered unnecessary.

1. Gillotin C, *et al.* No need to adjust the dose of 311C90 (zolmitriptan), a novel anti-migraine treatment in patients with renal failure not requiring dialysis. *Int J Clin Pharmacol Ther* 1997; **35:** 522–6.

Migraine and cluster headache. For comparison of the relative benefits of different triptans in migraine, see under Sumatriptan, p.627.

Further references.

1. Spencer CM, *et al.* Zolmitriptan: a review of its use in migraine. *Drugs* 1999; **58:** 347–74.
2. Bahra A, *et al.* Oral zolmitriptan is effective in the acute treatment of cluster headache. *Neurology* 2000; **54:** 1832–9.
3. Dowson AJ, Charlesworth B. Review of zolmitriptan and its clinical applications in migraine. *Expert Opin Pharmacother* 2002; **3:** 993–1005.
4. Charlesworth BR, *et al.* Speed of onset and efficacy of zolmitriptan nasal spray in the acute treatment of migraine: a randomised, double-blind, placebo-controlled, dose-ranging study versus zolmitriptan tablet. *CNS Drugs* 2003; **17:** 653–67.
5. Dowson AJ, *et al.* Tolerability and consistency of effect of zolmitriptan nasal spray in a long-term migraine treatment trial. *CNS Drugs* 2003; **17:** 839–51.
6. Lewis DW, *et al.* Adolescent Migraine Steering Committee. Efficacy of zolmitriptan nasal spray in adolescent migraine. *Pediatrics* 2007; **120:** 390–6.
7. Rapoport AM, *et al.* Zolmitriptan nasal spray in the acute treatment of cluster headache: a double-blind study. *Neurology* 2007; **69:** 821–6. Correction. *ibid.*; 2029.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Zomigon; ***Austral.:*** Zomig; ***Austria:*** Zomig; ***Belg.:*** Zomig; ***Braz.:*** Zomig†; ***Canad.:*** Zomig; ***Cz.:*** Zomig; ***Denm.:*** Zomig; ***Fin.:*** Zomig; ***Fr.:*** Zomig; Zomigoro; ***Ger.:*** AscoTop; ***Gr.:*** Zomigon; ***Hong Kong:*** Zomig; ***Hung.:*** Zomig; ***Irl.:*** Zomig; ***Israel:*** Zomig; ***Ital.:*** Zomig; ***Mex.:*** Zomig; ***Neth.:*** Zomig; ***Norw.:*** Zomig; ***Philipp.:*** Zomig; ***Pol.:*** Zomig; ***Port.:*** Zomig; ***Rus.:*** Zomig (Зомиг); ***S.Afr.:*** Zomig; ***Singapore:*** Zomig; ***Spain:*** Flezol†; Zomig; ***Swed.:*** Zomig; ***Switz.:*** Zomig; ***Thai.:*** Zomig; ***Turk.:*** Zomig; ***UK:*** Zomig; ***USA:*** Zomig; ***Venez.:*** Zomig.

Antimyasthenics

This chapter includes those drugs used for their anticholinesterase action in the treatment of myasthenia gravis and related neuromuscular disorders. Other groups of drugs playing an important role in the management of myasthenia are the corticosteroids (p.1490) and some drugs with immunosuppressant actions discussed in the chapters on Antineoplastics (p.635) and Immunosuppressants (p.1810).

Eaton-Lambert myasthenic syndrome

Eaton-Lambert myasthenic syndrome is a rare auto-immune disease of the neuromuscular junction. Unlike myasthenia gravis (below), in which autoantibodies affect acetylcholine receptors, antibodies in Eaton-Lambert syndrome act presynaptically to reduce release of acetylcholine. Weakness mostly affects the proximal muscles, particularly those of the limbs; respiratory and ocular muscles are usually spared. Autonomic symptoms including dry mouth, constipation, and impotence are common. Over half of patients also have small cell carcinoma of the lung. Successful treatment of the tumour often leads to some improvement in symptoms.

The symptomatic treatment of Eaton-Lambert syndrome involves the use of drugs that increase the availability of acetylcholine at the neuromuscular junction. Response to treatment with *anticholinesterases* alone is poor and treatment with *amifampridine*, which increases acetylcholine release, appears to be more effective, particularly when given with an anticholinesterase such as *pyridostigmine*. The use of similar drugs such as *guanidine* and *fampridine* is limited by severe adverse effects. Low-dose guanidine has been tried with pyridostigmine where amifampridine is not readily available. Although there has been some improvement with the combination, the incidence of adverse effects, especially gastrointestinal reactions, is still high. Immunosuppressants including *azathioprine* and *corticosteroids* are also used, and unlike in treatment for myasthenia gravis, corticosteroids do not appear to induce an initial exacerbation of symptoms. Plasma exchange or high-dose intravenous *normal immunoglobulin* have been tried in patients with severe weakness.

References.

1. Newsom-Davis J. Myasthenia gravis and the Lambert-Eaton myasthenic syndrome. *Prescribers' J* 1993; **33:** 205–12.
2. Oh SJ, *et al.* Low-dose guanidine and pyridostigmine: relatively safe and effective long-term symptomatic therapy in Lambert-Eaton myasthenic syndrome. *Muscle Nerve* 1997; **20:** 1146–52.
3. Seneviratne U, de Silva R. Lambert-Eaton myasthenic syndrome. *Postgrad Med J* 1999; **75:** 516–20.
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5. Sanders DB. Lambert-Eaton myasthenic syndrome: diagnosis and treatment. *Ann N Y Acad Sci* 2003; **998:** 500–8.
6. Newsom-Davis J. Lambert-Eaton myasthenic syndrome. *Rev Neurol (Paris)* 2004; **160:** 177–80.
7. Maddison P, Newsom-Davis J. Treatment for Lambert-Eaton myasthenic syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2005 (accessed 15/02/06).

Myasthenia gravis

Myasthenia gravis is an auto-immune disorder characterised by defective neuromuscular transmission and consequent muscular weakness. It is caused by the formation of autoantibodies to elements of the neuromuscular junction. In most patients, antibodies to the nicotinic acetylcholine receptor are present. However, about 10 to 15% of patients have so-called 'seronegative myasthenia', in whom antibodies to other elements such as muscle-specific tyrosine kinase (MuSK) may be present instead; the proportion of such patients is much higher among those with ocular myasthenia (disease confined to the extra-ocular muscles). The thymus appears to be involved in many patients and some have a thymoma. Classifications of the disease may be based on the distribution and severity of symptoms, on the age of onset, and on the presence or absence of thymoma. Other types of myasthenia include transient neonatal myasthenia due to transplacental passage of receptor antibodies, which may persist for 1 to 6 weeks in the infants of myasthenic mothers, penicillamine-induced myasthenia, and congenital myasthenia (see under Amifampridine, p.630).

Diagnosis of myasthenia gravis.

Antibody testing remains the gold standard for diagnosis of myasthenia gravis. Patients may often be tested first for their reaction to an anticholinesterase. Intravenous edrophonium preceded by atropine (Tensilon test) is the most commonly used anticholinesterase test because of its rapid onset and short duration of action. Severe adverse effects can occasionally occur so testing should only be undertaken when facilities for endotracheal intubation and controlled ventilation are immediately available. A positive result is considered to be a rapid but temporary increase in muscle strength. Repetitive nerve stimulation is also used as a diagnostic test but, like the anticholinesterase test, is not specific for myasthenia gravis. Computed tomography or magnetic resonance imaging may be used to detect thymoma.

Treatment of myasthenia gravis.

- Symptomatic treatment is with an *anticholinesterase*; pyridostigmine and neostigmine are those most commonly used. Most patients prefer pyridostigmine as it produces less muscarinic adverse effects and has a longer duration of action, although the quicker onset of action of neostigmine may offer an advantage at the beginning of the day. The dose must be adjusted to give the optimum therapeutic response but muscle strength may not be restored to normal and some patients must live with a degree of disability. The effect may vary for different muscles and the dosage should be adjusted so that the bulbar and respiratory muscles receive optimum treatment. Generally, anticholinesterases only provide partial remission and their effects tend to diminish with continued treatment. Overdosage may lead to a 'cholinergic crisis' (see Adverse Effects of Neostigmine, p.631). Edrophonium may be employed to establish whether the patient is underdosed or overdosed.
- *Corticosteroids* are the main immunosuppressive drugs used for treatment. They are also useful in patients with ocular myasthenia, who as a group respond poorly to anticholinesterases and to thymectomy, provided that their disability is severe enough to warrant long-term corticosteroid treatment with its attendant adverse effects. Many start with low doses such as 5 to 20 mg of prednisolone daily or on alternate days, to reduce the risk of steroid-induced exacerbations of weakness, and increase the dose slowly thereafter according to response; an improvement is usually seen after a few weeks. Others use more aggressive regimens to obtain a more rapid response and start with large doses such as 60 to 80 mg of prednisolone daily. Whichever method is used, once clinical benefit has been obtained the regimen should be modified to alternate-day dosage, with the dose being slowly tapered when the patient is in remission. Patients taking corticosteroids require less anticholinesterase therapy and, if the dosage of the anticholinesterase is not reduced, an initial deterioration in the myasthenia may occur in the first few weeks of treatment (see also under Interactions of Neostigmine, p.632). It is rarely possible to withdraw corticosteroids completely but some patients may be maintained satisfactorily on as little as 10 mg on alternate days. If remission cannot be maintained on low-dose prednisolone, addition of azathioprine at a dosage of 2 to 3 mg/kg daily may be considered.
- Addition of *azathioprine* to treatment may allow a reduction in the dose of both corticosteroids and anticholinesterases. Azathioprine may also be of use when corticosteroids are contra-indicated or when response to corticosteroids alone is insufficient, but it has a much slower onset of action than corticosteroids and is not usually used alone. *Ciclosporin* is effective in some patients unresponsive to standard combinations but serious adverse effects including nephrotoxicity may limit its use; the time to response is similar to that with corticosteroids. Other drugs such as *cyclophosphamide* and *methotrexate* have also been tried and benefit has been reported with *mycophenolate mofetil* and *tacrolimus*. However, a recent systematic review has found that only a small number of randomised controlled studies have been conducted on the use of immunosuppressive drugs for myasthenia gravis and most have been short-term. The review of this limited evidence concluded that, apart from cyclophosphamide used alone or ciclosporin used alone or with corticosteroids, there was no clear evidence of benefit from use of other immunosuppressants.
- Plasma exchange provides a dramatic but short-lived improvement and is useful as a short-term measure in myasthenic crisis to improve ill patients while other therapies take effect, but there is no evidence that repeated plasma exchange combined with immunosuppression is superior to immunosuppression alone. A similar short-term benefit has been seen from the use of high-dose intravenous *normal immunoglobulins*; however, a systematic review considered further study to be warranted.
- Thymectomy may be offered to all patients sufficiently fit to undergo surgery unless they have minimal symptoms, purely ocular disease, or late onset or seronegative disease. Thymectomy is usually avoided in prepubertal children because of concern over the effect on growth and the developing immune system; it has been suggested that symptomatic treatment with anticholinesterases should be continued until adolescence, when the disease often improves spontaneously. After thymectomy, remission or improvement may be expected in about 80% of patients without thymomas, although this may take some years; the response is poorer in those with thymomas.

References.

1. Evoli A, *et al.* A practical guide to the recognition and management of myasthenia gravis. *Drugs* 1996; **52:** 662–70.
2. Yi Q, Lefvert AK. Current and future therapies for myasthenia gravis. *Drugs Aging* 1997; **11:** 132–9.
3. Newsom-Davis J. Myasthenia gravis. *Prescribers' J* 2000; **40:** 93–8.
4. Vincent A, *et al.* Myasthenia gravis. *Lancet* 2001; **357:** 2122–8.
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7. Richman DP, Agius MA. Treatment of autoimmune myasthenia gravis. *Neurology* 2003; **61:** 1652–61.
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10. Kothari MJ. Myasthenia gravis. *J Am Osteopath Assoc* 2004; **104:** 377–84.
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12. Schwendimann RN, *et al.* Management of myasthenia gravis. *Am J Ther* 2005; **12:** 262–8.
13. Schneider-Gold C, *et al.* Corticosteroids for myasthenia gravis. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2005 (accessed 15/02/06).
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15. Hart IK, *et al.* Immunosuppressive agents for myasthenia gravis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 24/01/08).
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Ambenonium Chloride *(BAN, rINN)*

Ambenonii Chloridum; Ambénonium, Chlorure d'; Ambenoniumklorid; Ambenoniumkloridi; Ambestigmini Chloridum; Cloruro de ambenonio; Win-8077. *N,N'*-Oxalylbis(*N*-2-aminoethyl-*N*-2-chlorobenzyldiethylammonium) dichloride.

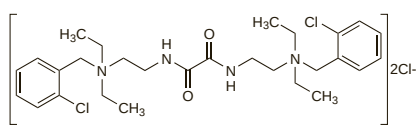
Амбенония Хлорид

$C_{28}H_{42}Cl_4N_4O_2$ = 608.5.

CAS — 7648-98-8 (ambenonium); 115-79-7 (anhydrous ambenonium chloride); 52022-31-8 (ambenonium chloride tetrahydrate).

ATC — N07AA30.

ATC Vet — QN07AA30.



Pharmacopoeias. In *Jpn.*

Adverse Effects, Treatment, and Precautions

As for Neostigmine, p.631.

Ambenonium produces fewer muscarinic adverse effects than neostigmine. As there is only slight warning of overdosage, routine use of atropine with ambenonium is contra-indicated be-