drug dose is decreased, the patient is advised to continue treatment for another 6–9 months, before attempting to titrate down therapy again. From experience, half of the patients are able to terminate drug therapy after intervention for one year and half will have to continue a longer period of drug therapy.

The most commonly used drugs for the prevention of migraine are the beta-blockers propranolol and metoprolol. Their use is supported by a good body of evidence from several placebo-controlled trials.[8-13] However, they have a disadvantage of significant side effects, such as sedation, decreased blood pressure and, especially in women, weight gain, which can make adherence to treatment a problem for many patients.[14] The success rate for beta-blockers is around 50%, with half of the patients experiencing significant decreases in the number and severity of migraine attacks.

In some European countries where the drug is licensed, another first-line choice is flunarizine, a calcium channel blocker. This drug is as effective as beta-blockers[15-17] but can lead to even greater weight gain than beta-blockers.

Certain AEDS have also shown efficacy in migraine prophylaxis. In Europe, topiramate is an AED that has been approved for the prevention of migraine. Sodium valproate, another AED that has shown evidence of efficacy in more than one placebo-controlled trial, is not licensed for this indication in Europe.[18-20]

The efficacy of topiramate in migraine prophylaxis has been confirmed in three large placebo-controlled studies.[21-23] Whilst sodium valproate has been shown to be effective in terms of the frequency of migraines, topiramate also influences the intensity and duration of attacks. Moreover, sodium valproate is also associated with weight gain. In contrast, topiramate is associated with no weight change or weight loss.[25]

In one US randomised, double-blind, placebo-controlled trial, topiramate demonstrated significant efficacy in migraine prevention within the first month of treatment, an effect that was maintained for the duration of the double-blind phase.[21] The 483 patients enrolled in the trial were aged 12–65 years, with a six-month history of migraine (International Headache Society criteria), and three to 12 migraines a month but no more than 15 headache days a month during a 28-day prospective baseline period. In the study, following a washout period, patients meeting the entry criteria were randomised to topiramate (50, 100, or 200mg/d) or placebo. Topiramate was titrated by 25mg per week for eight weeks to the assigned or maximum tolerated dose, whichever was less. Patients continued receiving that dose for 18 weeks. Mean monthly migraine frequency decreased significantly for patients receiving topiramate at 100mg/d and topiramate at 200mg/d vs placebo. In another US randomised, double-blind, placebo-controlled study, with a similar design and patient population, topiramate, 100 or 200mg/d, was shown to be effective as a preventive therapy for patients with migraine. Significantly more topiramate-treated patients exhibited a 50% or more reduction in monthly migraine frequency than placebo-treated patients.[23] A multinational randomised, double-blind, multicentre trial evaluated the efficacy and safety of topiramate (100 or 200mg/d) vs placebo for migraine prophylaxis, with propranolol as an active control. The study population included patients with episodic migraine with and without aura. In the study, the lower dose of topiramate and propranolol exhibited similar efficacy profiles.[22] Topiramate was also superior to placebo. The efficacy of results from eight-month open-label extension phases of two pivotal, six-month, randomised, double-blind, placebo-controlled trials with topiramate, demonstrated there was persistent reduction in monthly migraine frequency that was consistent with the initial six-month maintenance period.[24]

Topiramate demonstrated good tolerability across all three pivotal trials in migraine prevention at the target dose of 100mg/d. A common side effect seen with topiramate is paresthesia, however, this will normally go away after a few days. Cognitive side effects appear in 8–10% of patients, which can potentially restrict the use of topiramate. These persistent cognitive problems include memory problems and problems with concentration. If these situations arise, then treatment should be stopped. However, careful titration of topiramate can help ameliorate side effects. A typical titration would begin with an initial low dose of 25mg/day for the first week. The dosage should then be increased at one- or two-week intervals. This will help to improve tolerability.

Summary

Migraine is a severe disruption to everyday life. Moreover, it has a major economic impact, in terms of absence from work, particularly in women. The indirect costs in terms of work days lost are much higher than direct costs related to drug treatment.

Currently the number of patients receiving migraine prophylaxis treatment is still too low compared to the real need. The statistics show that only 15–20% of all migraine patients that fulfil the criteria for migraine prophylaxis treatment receive the appropriate treatment. This is partly due to some doctors not being aware of the treatment options available. Another problem is that patients may underestimate the impact of migraine.

In terms of drug class of choice, if there are no contra-

indications, then beta-blockers should be used, especially as these drugs are backed by good clinical data and are readily available as cheap generics.

However, if the patient has contra-indications for beta-blockers (asthma, fatigue, obesity, depression) or beta-blockers do not appear to be effective, then topiramate offers new hope for patients with frequent migraine in terms of controlling their condition and improving their quality of life. ■

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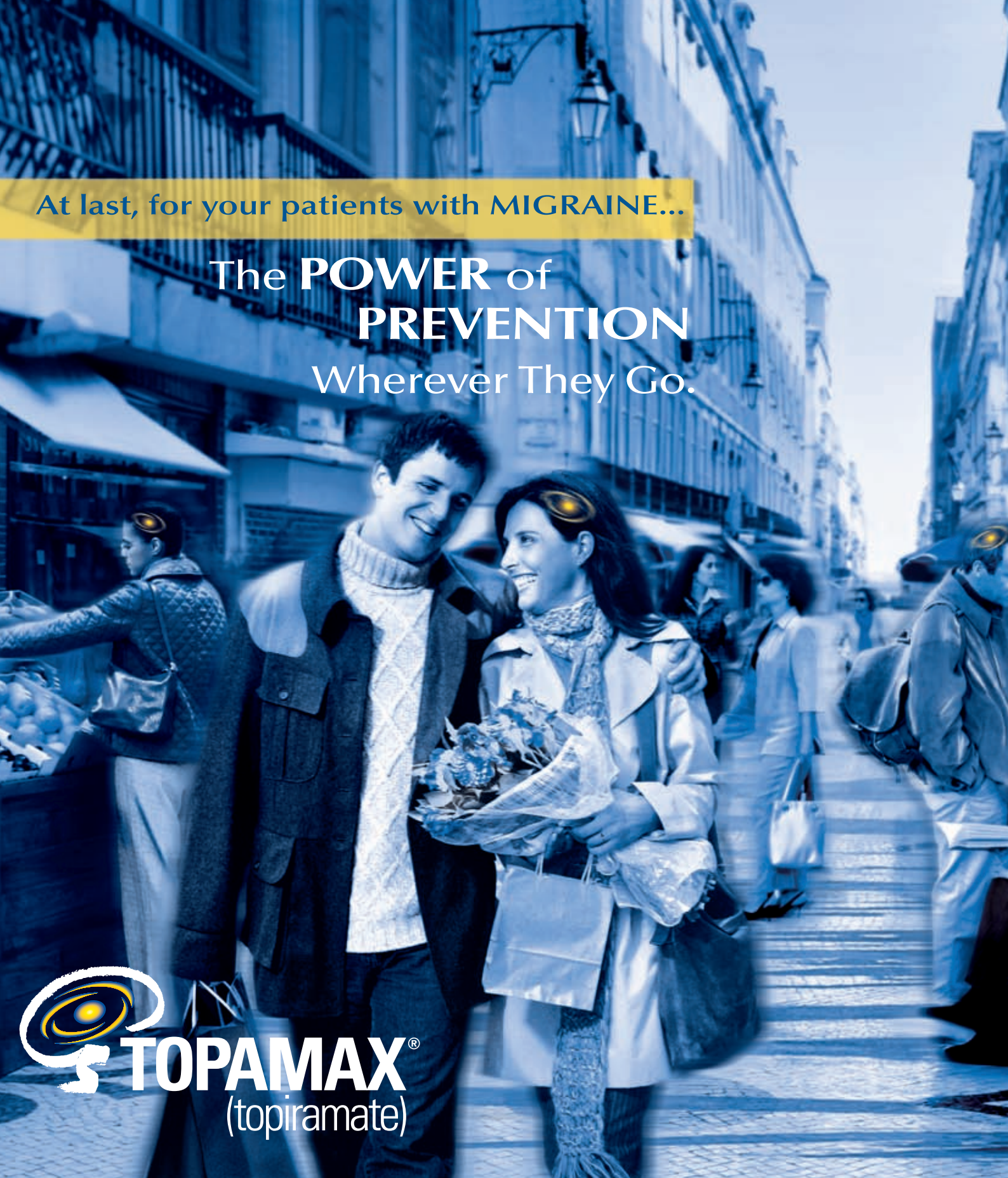

TOPAMAX® Abbreviated Prescribing Information. Please read Summary of Product Characteristics before prescribing. Presentation: Tablets: 25, 50, 100, 200 mg topiramate. Sprinkle Capsules: 15, 25, 50 mg topiramate. **Uses: Epilepsy:** *Monotherapy:* Newly diagnosed epilepsy (age≥6 years): generalised tonic-clonic/partial seizures, with/without secondarily generalised seizures. *Adjunctive therapy of seizures:* partial, Lennox Gastaut Syndrome and primary generalised tonic-clonic. Conversion from adjunctive to monotherapy: efficacy/safety not demonstrated. **Migraine:** Prophylaxis. **Dosage and Administration:** Oral. Do not break tablets. Low dose initially; titrate to effect. Renal disease may require dose modification. **Epilepsy:** *Monotherapy:* Over 16 years: Initial target dose: 100 mg/day (two divided doses; maximum 400 mg/day). Children 6 to 16: Initial target dose: 3 – 6 mg/kg/day (two divided doses). Initiate at 0.5 – 1 mg/kg nightly with weekly or fortnightly increments of 0.5 – 1 mg/kg/day. Doses less than 25 mg/day: Use Topamax Sprinkle Capsules. *Adjunctive therapy:* Over 16 years: Usually 200-400 mg/day (two divided doses; maximum 800mg/day). Initiate at 25 mg daily with weekly increments of 25 mg. Children 2 to 16: Approx. 5 - 9 mg/kg/day (two divided doses). Initiate at 25 mg nightly with weekly increments of 1 - 3 mg/kg. **Migraine:** Over 16 years: Usually 100 mg/day (two divided doses; maximum 100 mg day). Initiate at 25 mg nightly with weekly increments of 25 mg. Longer intervals can be used between dose adjustments. Children to 16: Not studied.Sprinkle Capsules: take whole or sprinkle on small amount (teaspoon) of soft food and swallow immediately. **Contra-indications:** Hypersensitivity to any component. **Precautions and Warnings:** Withdraw gradually. Renal impairment delays achievement of steady-state. Caution with hepatic impairment. May cause sedation; so caution if driving or operating machinery. Acute myopia with secondary angle-closure glaucoma reported rarely; symptoms typically occur within 1 month of use and requires discontinuation of Topamax and treatment of symptoms. Increased risk of renal stones. Adequate hydration is very important. Food supplement may be required. Bicarbonate level may be decreased so monitor patients with conditions/drugs that predispose to metabolic acidosis and reduce dose/discontinue Topamax if acidosis persists. **Migraine:** Reduce dosage gradually over at least 2 weeks before discontinuation to minimise rebound headaches. Significant weight loss may occur during long-term treatment. Regularly weigh and monitor for continuing weight loss. **Interactions:** Possible with phenytoin, carbamazepine, digoxin, hydrochlorothiazide, pioglitazone, oral contraceptives, haloperidol and metformin. Decrease in serum bicarbonate levels. **Pregnancy:** If benefits outweigh risks. Discuss possible effects and risks with patient. Contraception recommended for women of childbearing potential (oral contraceptives should contain at least 50µg oestrogen). **Lactation:** Avoid. **Side Effects:** Abdominal pain, ataxia, anorexia, anxiety, CNS side effects, diarrhoea, diplopia, dry mouth, dyspepsia, headache, hypoaesthesia, fatigue, mood problems, nausea, nystagmus, paraesthesia, weight decrease, agitation, personality disorder, insomnia, increased saliva, hyperkinesia, depression, apathy, leucopenia, psychotic symptoms (such as hallucinations), venous thrombo-embolic events, nephrolithiasis, increases in liver enzymes. Isolated reports of hepatitis and hepatic failure when on multiple medications. Acute myopia with secondary acute-angle closure glaucoma, reduced sweating (mainly in children), metabolic acidosis and suicidal ideation or attempts reported rarely. Bullous skin and mucosal reactions reported very rarely. Not all indications are approved in all countries. Full prescribing information available on request. Janssen Pharmaceutica N.V., Turnhoutseweg 30, B-2340 Beerse, Belgium

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