Bisoprolol

REJECTED

The Expert Committee, after evaluation, declines to list the medicine proposed in the application.
The Model List of Essential Medicines reports reasons that Committee Members have identified for denying listing.

Section: 5. Medicines for neurological disorders > 5.1. Medicines for central nervous system disorders > 5.1.5. Medicines for headache disorders > 5.1.5.2. Medicines for migraine prophylaxis

ATC codes: C07AB07

Indication	Migraine ICD11 code: 8A80.Z
INN	Bisoprolol
Medicine type	Chemical agent
List type	Core
Formulations	Oral > Solid: 1.25 mg ; 5 mg
EML status history	Application rejected in 2025 (TRS 1064)
Sex	All
Age	Adolescents and adults
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Patents have expired in most jurisdictions Read more about patents.
Wikipedia	Bisoprolol
DrugBank	Bisoprolol

Expert Committee recommendation

The Expert Committee noted that migraine is a common primary headache disorder characterized by recurrent moderate to severe pain and acknowledged the public health relevance of effective treatments. Migraine is a cause of considerable disability and results in a substantial socioeconomic burden, which is greater for women than for men. Migraine prophylaxis is generally recommended in the presence of at least four migraine days per month and/or when migraine substantially affects quality of life. The Committee noted that several classes of medication are commonly used for migraine prophylaxis, including antidepressants, anticonvulsants, antihypertensives and calcitonin gene-related peptide (receptor) monoclonal antibodies. Currently, the Model Lists include only propranolol for migraine prophylaxis. The Committee noted that the only evidence for bisoprolol presented in the application was a single randomized controlled trial that compared oral bisoprolol 5 mg or 10 mg to placebo over a treatment period of 12 weeks in people with migraine and that this trial was at serious risk of bias. The trial showed a significant reduction in the frequency of migraine attacks but no effect on the duration and severity of the attacks. No studies comparing propranolol with bisoprolol are available. The Committee noted that bisoprolol and propranolol differ in their pharmacokinetic properties (e.g. half-life, duration of action). the potential advantage of a reduced frequency of dosing with bisoprolol may be offset by a prolonged-release formulation of propranolol. The Committee accepted the known safety profile and contraindications of beta-blockers. Data on safety of propranolol and bisoprolol for the prophylaxis of migraine are limited, however no additional serious safety signals emerge. The Committee acknowledged that the benefit of beta blockers for episodic migraine seems to be a class effect, but that most data and the highest quality data are available for propranolol. The Committee considered that the data presented for bisoprolol were too limited and of inadequate quality to support EML listing. Based on these considerations, the Expert Committee did not recommend the inclusion of bisoprolol on the EML as a therapeutic alternative to propranolol due to there being inadequate evidence for comparative benefit.

Background

The application proposed an extension of the indications for the listing of bisoprolol on the core list of the EML to include migraine prophylaxis in adults as a therapeutic alternative to propranolol. Bisoprolol has not previously been evaluated for inclusion on the EML for migraine prophylaxis. It is currently listed for use in the treatment of cardiovascular conditions (angina, arrhythmias, hypertension and heart failure). Propranolol is currently included in the EML for migraine prophylaxis.

Public health relevance

Migraine is a prevalent neurovascular disorder characterized by moderate to severe headache attacks, often accompanied by nausea, vomiting, photophobia/phonophobia and sensitivity to external stimuli (light, noise, odours). Symptoms are disabling and affect participation in life activities, quality of life and productivity (1). In around 25% of those affected, episodes may be preceded by transient focal neurological symptoms – most commonly visual disturbances, less commonly paresthesias, rarely motor or language deficits. The global prevalence of migraine is estimated at 14–15% (more than 1 billion people worldwide), and it is two to three times higher in women than men (2). According to the Global Burden of Disease study 2021, migraine was the fourth highest cause of years lived with disability at level 4 (3). In an analysis of the Global Burden of Disease study 2016, migraine accounted for 45.1 million disability-adjusted life years (4). Around 2–3% of people with episodic migraine (headache on < 15 days/month) transition to more disabling chronic migraine (headache on ≥ 15 days/month of which a majority are with symptoms of migraine) (5). One of the main risk factors for the transition to chronic migraine is poorly managed acute treatment and the overuse of acute medications (6).

Benefits

The applicants conducted a systematic literature review and meta-analysis of randomized controlled trials of beta-blockers in migraine prophylaxis. For the analysis of efficacy, the outcome measures considered were: persisting monthly headache/migraine days, defined as the residual days reported by patients at the end of treatment; change in monthly headache/migraine days, defined as the variation in days reported by patients from baseline to the end of follow-up; and responder rate, defined as the proportions of patients reporting a ≥ 50% reduction of monthly headache/migraine days or monthly attacks compared with baseline. The application presented the results for propranolol and bisoprolol, both versus placebo, only. No studies were identified that compared propranolol and bisoprolol. Propranolol Ten randomized controlled trials comparing propranolol with placebo for migraine prophylaxis were identified, eight of which did not report the predefined efficacy outcomes (7–14). Of the remaining two, one was a placebo-controlled trial which evaluated topiramate for prophylaxis in episodic migraine with propranolol as an active control arm (15). The other was a comparative study of candesartan versus propranolol for migraine prophylaxis without distinction between episodic and chronic (16). In the randomized controlled trial in episodic migraine, for the outcome of change in monthly migraine days, there was low-certainty evidence that propranolol 160 mg was superior to placebo (standardized mean difference (SMD) −0.27, 95% confidence interval (CI) −0.51 to −0.04; one randomized controlled trial, 286 participants). For the outcome of ≥ 50% responder rate, there was low-certainty evidence that propranolol 160 mg was superior to placebo (risk ratio (RR) 1.97, 95% CI 1.37 to 2.83; one randomized controlled trial, 286 participants). In the randomized controlled trial without distinction between episodic and chronic migraine, there was moderate-certainty evidence of no significant difference between propranolol 160 mg and placebo for persisting monthly migraine days (SMD −0.31, 95% CI −0.67 to 0.05; one randomized controlled trials, 120 participants) or of ≥ 50% responder rate (RR 1.71, 95% CI 0.99 to 2.98; one randomized controlled trial, 120 participants). From the remaining studies, there was low-certainty evidence of benefits of propranolol 80 mg (RR 2.17, 95% CI 1.06 to 4.42; one randomized controlled trial, 36 participants) and 160 mg (RR 2.00, 95% CI 1.37 to 2.92; one randomized controlled trial, 72 participants) over placebo for ≥ 50% responder rate, and of propranolol 160 mg over placebo for persisting monthly migraine attacks, however for this outcome, the difference was not significant (SMD −1.00, 95% CI −2.00 to 0.01; four randomized controlled trials, 334 participants). Bisoprolol One randomized controlled trial (152 participants) was identified comparing bisoprolol 5 mg or 10 mg with placebo as prophylaxis in patients with migraine without distinction between episodic and chronic (17). For the outcome of persisting monthly migraine days, there was very-low-certainty evidence for benefit of bisoprolol 5 mg (SMD −0.38, 95% CI −0.70 to −0.06) and bisoprolol 10 mg (SMD −0.36, 95% CI −0.68 to −0.04) over placebo. For the outcome of the change in monthly migraine days, there was very-low-certainty evidence for benefit of bisoprolol 5 mg and 10 mg (SMD 0.34, 95% CI 0.02 to 0.66).

Harms

Adverse effects associated with beta-blockers are well known and can be significant. Effects vary within the class depending on the cardioselectivity of the medicines. Contraindications include use in people with asthma, congestive heart failure and depression. From the randomized controlled trial comparing bisoprolol and placebo, the most frequently reported adverse events were fatigue and dizziness, with the difference between bisoprolol and placebo for dizziness being statistically significant. Heart rate, and systolic and diastolic blood pressure were significantly lower in the bisoprolol groups than in the placebo group (17).

Additional evidence

A 2019 systematic review and network meta-analysis of 158 randomized controlled trials evaluated the efficacy of beta-blockers in preventing migraine and tension-type headache (18). The results of the network meta-analysis found high-quality evidence that propranolol is better than placebo, but found no significant differences between beta-blockers (propranolol, bisoprolol, metoprolol, timolol and nadolol) for the outcomes of headache frequency at 8 weeks and 12 weeks.

Cost / cost effectiveness

The application stated that no published studies existed on the cost–effectiveness of propranolol or bisoprolol for migraine prevention. The application and presented a new modelled cost–effectiveness assessment comparing bisoprolol 5 mg daily with propranolol 160 mg. Costs per healthy life year gained were 136 United States dollars (US$) for bisoprolol and US$ 417 for propranolol. Incremental cost–effectiveness modelling found propranolol to be dominated by bisoprolol. The analyses were sensitive to medicine costs. The application highlighted the wide uncertainties in the analyses due to the poor quality of the trial data used in the model.

WHO guidelines

WHO guidelines for migraine prophylaxis are not currently available. The application provided a brief summary of recommendations involving beta-blockers for migraine prophylaxis from various national and international guidelines.

Availability

Bisoprolol has wide global regulatory approval and market availability. Generics are available in most countries.

Other considerations

The Department of Mental Health, Brain Health and Substance Use provided comments on the application. The technical department acknowledged the limitations of the evidence presented in the application but advised that including bisoprolol as an alternative to propranolol on the EML could potentially support countries in prioritizing its inclusion in national policies and procurement plans, which may help to improve appropriate use, availability and affordability.

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