1. Summary statement

For acute migraine therapy the following additions to the list are proposed:

a) sumatriptan 50 mg
b) ibuprofen 200 mg for children and adolescents

2. Name of the focal point in WHO supporting the application:

Dr Tarun Dua
Programme for Neurological Diseases and Neuroscience
Evidence, Research and Action on Mental and Brain Disorders (MER)
Department of Mental Health and Substance Abuse, WHO, Geneva


4. a) Sumatriptan
   b) Ibuprofen (for children and adolescents)

5. a) Sumatriptan tablets 50 mg
   b) Ibuprofen tablets 200 mg

6. a) Sumatriptan 50 mg is available in more than 110 countries (GSK, personal communication), and has been increasingly available in generic formulations since May 2006. Manufacturer: GSK and generic companies.
   b) Ibuprofen is generic and available worldwide.

7. Listing is requested as individual medicines.

8. a) Eleven percent of the world’s adult population suffer from migraine [Stovner et al 2007]. Migraine was listed by WHO in the Global Burden of Disease Study 2000 as the 19th highest cause of disability (12th in women) [World Health Report 2001 at www.WHO.int]. The burden of illness is high because, whilst it affects all ages, it is most disabling to those aged 35-45 years – a productive period of life. An estimate of the total cost of migraine in Europe is € 27 billion per year [Andlin-Sobocki et al 2005]. Whilst this largely reflects the high indirect costs incurred in developed countries, sufficient evidence exists that migraine is ubiquitous and imposes similar levels of ill-health in all continents and in developing as well as developed countries [Stovner et al 2007]. Only in Africa may it be significantly less common, but very few studies have been conducted to show this. Therefore, migraine has been acknowledged by WHO as a priority for effective treatment [World Health Organization 2006].
b) In children and adolescents, migraine is less prevalent and not associated with the high level of indirect costs arising from lost productivity. Nonetheless, its prevalence in those aged 6-18 years probably exceeds 6% worldwide [Stovner et al 2007], it is a debilitating and disabling condition in this age group, and can adversely affect education. Over two-thirds of children with migraine attacks interrupt their normal activities, whilst 970,000 self-reported migraineurs aged 6-18 years in the US lost 329,000 schooldays per month [Robertson WC 2008]. Children and adolescents therefore deserve efficacious treatment of their migraine no less than adults.

9. a) Sumatriptan is used in a single oral dose of 50 mg. Repeated dosing after 2 hours is unhelpful when the first dose is ineffective [Ferrari 1994]. A second dose may be required for symptom recurrence (relapse) within 6-48 hours.

The principal problem with this drug, and others of its class (triptans), is medication-overuse headache resulting from chronic over-frequent usage [Tfelt-Hansen & Steiner 2007]. This problem is likely to arise with regular use on 10 or more days per month, which is rarely appropriate. It can be avoided by limiting usage to less than this [Diener & Limmroth 2004].

b) Ibuprofen is given in an oral dose of 7.5-10 mg/kg, which may be repeated 4-hourly.

10+11 Sumatriptan

Aspirin and paracetamol are probably the most commonly used drugs for migraine worldwide. The efficacy of aspirin has been proven. It is best used in soluble form, in which it has demonstrated superiority over placebo in randomised clinical trials (RCTs) with efficacy rates in terms of headache relief at 2 hours of 46-56% [Tfelt-Hansen & Rolan 2006; Lampl 2007]. Evidence-based guidelines [eg, British Association for the Study of Headache 2007], and the principles of management published by Lifting The Burden under the imprimatur of WHO and in collaboration with the European Headache Federation (which distil the various published guidelines within Europe) [Steiner et al 2007], recommend that soluble aspirin should be the first-line drug for the treatment of migraine attacks.

This efficacy rate of 46-56% indicates that, on the conservative measure of headache relief at 2 hours, about half of patients using aspirin will not benefit. For these, there is a clear need for a second-line alternative.

Whilst some headache experts believe that triptans are clinically more effective than aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs) for acute migraine [Lipton et al 2004a; Lipton et al 2004b], RCTs have had difficulty showing this. In several, aspirin, with its 2-hour headache relief rates of 46-56%, has been as effective as sumatriptan 50 mg (2-hour headache relief rates: 48-55%) [Tfelt-Hansen et al 2000; Diener et al 2004a; Diener et al 2004b; Lampl et al 2007]. Furthermore, oral sumatriptan 50 mg is associated with an 8% (95% CI: 2-14%) higher rate of adverse events than placebo [Ferrari et al 2001; Ferrari et al 2002], although these are rarely serious and generally mild to moderate (the triptan class-symptoms of tingling, numbness, warm/hot sensations and feelings of pressure or tightness in different parts of body – including the chest and neck – which are non-cardiac in origin). This evidence supports the continued recommendation that aspirin is first-line treatment, but does not indicate that sumatriptan 50 mg offers no benefits where aspirin has failed. Clearly, neither drug is universally effective according to headache relief rates, but it is unlikely that non-responders to aspirin are the same as the non-responders to triptans. Since the modes of action of these treatments are fundamentally different, there is no reason why they should
be the same; furthermore, widespread clinical experience does not suggest they are the same. In fact, there is some direct evidence that eletriptan, for example, is effective in non-responders to other treatments [Chia et al 2003; Diamond et al 2004]. Whether the reverse is true – that aspirin is effective in triptan non-responders – has not been adequately investigated and probably never will be.

Therefore, in a stepped-care approach with aspirin as first line, sumatriptan 50 mg as the second step is likely extend efficacy to some 45-55% of those who do not find it with aspirin, bringing benefit to up to 80% of patients overall.

We argue that a migraine-specific triptan is the appropriate second step for non-responders to aspirin. Other NSAIDs, having similar action, are unlikely to be more than marginally better. Paracetamol is generally not a useful alternative, and in our view should be deleted from the essential medicines list as its efficacy is poorly supported by contradictory evidence [Leinisch et al 2005; Lipton et al 2000] and it is not recommended by WHO-endorsed principles of management [Steiner et al, 2007]. The likely alternative would be narcotics, but these cannot be recommended for migraine treatment because of their abuse potential.

On the issue of which triptan, the differences between triptans are not major [Tfelt-Hansen et al 2000]. All have efficacy that is clearly superior to that of placebo, demonstrated in many high-quality trials with very high levels of statistical significance [Ferrari et al 2001]. For sumatriptan 50 mg, for example, 2-hour headache relief rate is 48-55% [Tfelt-Hansen et al 2000; Diener et al 2004a; Diener et al 2004b] with a mean therapeutic gain (difference from placebo) estimated by RCT meta-analysis of 32% (95 CI: 26-38%) [Ferrari et al 2001; Ferrari et al 2002]. The tolerability differences between triptans are small, and generally dose-related. Sumatriptan 50 mg is associated with an 8% (95% CI: 2-14%) higher rate of adverse events than placebo [Ferrari et al 2001; Ferrari et al 2002], and a number-needed-to-harm (NNH), therefore, of 12.5. These events, rarely serious and generally mild to moderate, are the triptan class-symptoms of tingling, numbness, warm/hot sensations and feelings of pressure or tightness in different parts of body – including the chest and neck – which are non-cardiac in origin. We recommend sumatriptan 50 mg for inclusion in WHO’s list of essential medicine as second line for acute migraine, rather than any other triptan, for five main reasons:

1. multiple well-conducted trials in large numbers of patients supported its development;
2. the side-effect profile of sumatriptan 50 mg is such that, based on its safety and tolerability, it is now available from pharmacists without prescription in UK [Tfelt-Hansen & Steiner 2007].
3. evidence of safety is supported by post-marketing experience derived from use of sumatriptan in more than 700 million doses worldwide;
4. sumatriptan 50 mg is already available in more than 110 countries;
5. sumatriptan is now generic and its cost is lowest among triptans.

Ibuprofen for children and adolescents
Children and adolescents deserve efficacious treatment of their migraine no less than adults, but their options are different. In children and younger adolescents, aspirin use has been associated with Reye’s syndrome, and it is therefore contraindicated. The current essential medicines list offers only paracetamol, but again the evidence for this drug is relatively poor. In one RCT [Hämäläinen et al 1997a], the therapeutic gain over placebo for 2-hour headache relief was 31% in ibuprofen-treated children but only 17% in the paracetamol group. Triptans are not the solution in these age groups: oral treatment has been assessed with sumatriptan [Hämäläinen et al 1997b], rizatriptan [Winner 2002] and zolmitriptan (a trial in 850 patients) [Rothner et al 2006] and found to be without benefit
only in one small trial of 32 patients was zolmitriptan superior to placebo [Evers et al 2007]. Specifically in adolescents, only intranasal administration has demonstrated efficacy, both for sumatriptan and zolmitriptan [Lewis et al 2004; Hämäläinen 2006, Lewis et al 2007]. On the other hand, ibuprofen in doses of 7.5-10 mg/kg has been shown in two RCTs to be superior to placebo in children and adolescents [Hämäläinen 1997a, Lewis et al 2002; Lewis et al 2004; Hämäläinen 2006].

We argue therefore for inclusion of ibuprofen 200 mg in WHO’s list of essential medicine for the treatment of acute migraine in children and adolescents.

12. The cost of sumatriptan 50 mg is, generally, significantly higher than that of aspirin (or of a range of other generic NSAIDs). These drugs cost very little as solid tablets; but in effervescent formulations, which are preferred for faster onset of action, this is not the case: prices may exceed USD 1 per dose. Moreover, whereas sumatriptan until recently had the highest cost of all triptans (except in countries where local drug law did not provide patent protection), from 2006, with patent expiry, many generic formulations have become available and brought competitive reductions in cost. Sumatriptan is now amongst the least expensive of triptans, in some countries already well below USD 2 per dose. This price can be expected to fall further with increased availability.

Cost-comparisons between aspirin and sumatriptan are not directly relevant if one is first-line and the other second-line. However, the following theoretical pharmacoeconomic example illustrates the potential cost-benefit of sumatriptan 50 mg:

a. if cost of 1 dose of sumatriptan is USD 1.50;
b. efficacy (ability to return to work) in those who use it = 50%;
c. return to work recovers half a lost day;
d. then sumatriptan is cost-saving if a day is worth > USD 6.

15. Proposed text for the WHO Model Formulary:
For acute treatment of migraine:
Adults: aspirin as first line; sumatriptan 50 mg as second line. Children and adolescents: ibuprofen 200 mg.

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On behalf of Lifting The Burden: the Global Campaign to Reduce the Burden of Headache Worldwide.

P.Tfelt-Hansen
Consultant in Neurology,
Chairman, International Headache Society Standing Commitee on Clinical Trials
Danish Headache Centre
Department of Neurology
University of Copenhagen
Glostrup Hospital
Glostrup Denmark
T. Steiner
Chairman, Lifting The Burden: the Global Campaign to Reduce the Burden of Headache Worldwide
Division of Neuroscience and Mental Health
Imperial College London
London, UK

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