

07.00.00.00 - ANTIMIGRAINE MEDICINES

1. Summary statement

For acute migraine therapy the following new medicine is proposed:
Sumatriptan 50 mg.

2.

3. Global Campaign to Reduce the Burden of Headache Worldwide, a joint venture between WHO, EHF, WHA, and IHS.

4. Sumatriptan.

5. Sumatriptan tablets 50 mg.

6. Sumatriptan is available in more than 110 countries (GSK, personal communication)

Manufacturer: GSK.

Sumatriptan 50 mg is generic from May 2006.

7. Listing is requested as individual medicine.

8. Eleven percent of the world's adult population suffer from migraine (www.WHO.int). Whilst it is most disabling to those aged 35-45 years, migraine can also trouble much younger people, including children. Migraine is listed by WHO as the 19th highest cause of disability (12th in women) in the Global Burden of Disease Study 2000 (www.WHO.int). It is estimated that the total annual cost of migraine is 27 billion Euros per year in Europe [1]. 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 everywhere [2], making it a priority for effective treatment.

9. Sumatriptan is used in a single oral dose of 50 mg (repeat dosing after 2 hours is useless if the first dose is ineffective [3]). A second dose may be required for symptom recurrence (relapse) within 6-48 hours.

The principal problem with drugs of this class (triptans) is medication-overuse headache resulting from chronic over-frequent usage [4,5]. In order to avoid this problem sumatriptan should not be used on more than 9 days per month maximum [4].

10+11 Sumatriptan (a triptan)

In our view a specific antimigraine drug is needed in acute migraine treatment. Non-specific symptomatic drugs (acetylsalicylic acid with or without an anti-emetic such as metoclopramide) are very useful in managing the acute attack but effective only in about 50% of patients [6]. All other patients are likely to need specific medication. Triptans (5-HT_{1B/1D} receptor agonists) are of proven efficacy and well established as antimigraine drugs (for reviews see [7, 8, 9, 10, 11, 12, 13, 14, 15]). Nevertheless, it has been difficult to show superiority of triptans over other medicines

apart from ergotamine in RCTs, and the possible reasons for this have been discussed [16]. Thus, in comparative RCTs, oral sumatriptan 100 mg, rizatriptan 10 mg and eletriptan 40 mg were all superior to oral ergotamine 2 mg [17,18,19]. In contrast, rectal ergotamine 2 mg was superior to sumatriptan 25 mg (Trial Register, www.GSK.com). Sumatriptan 100 mg was not superior to aspirin plus metoclopramide in two RCTs [20, 21] whilst a new formulation of buffered aspirin 1000 mg was equivalent in efficacy to sumatriptan 50 mg [22]. Recently, it was shown that sumatriptan 100 mg (75% for headache relief) was superior to tolfenamic acid 200 mg (58%) [22]. Despite these findings, extensive clinical experience informs us that many patients who do not respond to symptomatic medication will derive substantial benefit from, and only from, specific medication.

There are seven oral triptans on the market: sumatriptan 50-100 mg, zolmitriptan 2.5-5 mg, naratriptan 2.5 mg, rizatriptan 5-10 mg, almotriptan 12.5 mg, eletriptan 20-80 mg and frovatriptan 2.5 mg. The choice between them should be based on safety, efficacy and tolerability in randomised clinical trials (RCTs) and on clinical experience with them. Ideally, all triptans should be directly compared to each other in head-to-head RCTs [14] in general population (rather than specialist clinic) patient samples in order to select the optimum one, and its dose, for the List of Essential Medicines. These trials have mostly not been done, but triptans have been compared in several meta-analyses [8,7,9,10] of which the meta-analysis by Ferrari et al 2002 [10] is the most extensive. The comparisons of triptans below concerning efficacy and tolerability are based on head-to-head RCTs and on this meta-analysis [10]. In addition, safety and possible drug interactions are taken into account.

The triptans are generally safe drugs and in a recent consensus statement it was stated that the incidence of serious cardiovascular events with triptans in clinical trials and in clinical practice appears to be extremely low [24]. Rizatriptan interacts with propranolol (which is commonly used for migraine prophylaxis), causing an increase in rizatriptan concentration [25]. Therefore a lower dose of rizatriptan (5 mg) is recommended rather than the standard dose of 10 mg in migraine patients on propranolol. The concentration of eletriptan is increased by concomitant use of potent CYP3A4 inhibitors [14], and combined use of the two is not recommended. Many drugs that are potent CYP3A4 inhibitors are used for a variety of medical conditions, whilst not being recognised as such by prescribers or users. Because of these possibilities for drug-interactions, rizatriptan and eletriptan are not ideal candidates for the List of Essential Medicines.

Naratriptan 2.5 mg and frovatriptan 2.5 mg are both of relatively low efficacy [9,10] with lower therapeutic gain (TG) than sumatriptan 100 mg either in meta-analyses [9,10] or head-to-head comparative RCTs [26]. Naratriptan was in addition inferior to rizatriptan 10 mg [27] and eletriptan 40 mg [28]. These drugs are therefore poor candidates for the List of Essential Medicines. Zolmitriptan 2.5 mg was comparable to sumatriptan 100 mg in meta-analyses [8,9] with a TG for pain-free after 2 hours of 20%, and 16% more adverse events (AEs) than placebo [10]. Zolmitriptan 5 mg was comparable to sumatriptan 100 mg in one comparative RCT [29]; but zolmitriptan 2.5 mg, which is the clinically used dose, has not been compared to other triptans in head-to-head comparisons. The relative merits of zolmitriptan 2.5 mg are therefore difficult to judge.

Remaining candidates are sumatriptan and almotriptan. The dose of sumatriptan used in most RCTs was 100 mg, and this was chosen as the standard with which to compare other triptans in the

meta-analyses [9,10]. Furthermore, sumatriptan 100 mg was chosen as the comparator in most comparative RCTs [10,11]. Although in a Cochrane review sumatriptan 50 mg was not superior to placebo, only a small number of patients (n=124) were included in this analysis [11]. In a large meta-analysis sumatriptan 50 mg was superior to placebo, with a TG of 18% for pain free after 2 hours [9], and sumatriptan 50 mg was as effective as sumatriptan 100 mg on this measure both in the meta-analyses [9,10] and in a head-to-head comparative RCT [30] whilst causing fewer AEs (8% vs. 16%) than sumatriptan 100 mg. The incidence of AEs after sumatriptan 50 mg was similar to that after placebo in this large RCT [30]. In a systematic review of six placebo-controlled RCTs with early treatment of migraine attacks, sumatriptan 100 mg (58% pain-free after 2 hours) was superior to sumatriptan 50mg (49%) [31] but 100 mg caused more AEs (15% of patients treated) than sumatriptan 50 mg (10%). From a clinical point of view, 50 mg appears to be the optimum dose for sumatriptan.

In the meta-analysis, almotriptan was superior to placebo with a similar TG to that of sumatriptan (21%) for pain free after 2 hours [10]. Sumatriptan 50 mg caused about 8% more AEs than placebo or almotriptan 12.5 mg [10]. Completed later and not included in this meta-analysis, a large comparative RCT of sumatriptan vs almotriptan showed sumatriptan 50 mg (58%) and almotriptan 12.5 mg (57%) were similar for headache relief at 2 hours whereas sumatriptan (25%) was superior to almotriptan (18%) for pain-free after 2 hours ($p=0.005$) [32]. Sustained pain-free over 24 hours was higher after sumatriptan 50 mg (18%) than after almotriptan 12.5 mg (13%) [33]. Sumatriptan (19%) caused slightly more AEs than almotriptan (15%) ($p=0.06$) [31].

The choice is between two candidates for an oral triptan: almotriptan 12.5 mg and sumatriptan 50 mg. Pain-free after 2 hours is recommended as the primary efficacy measure by the Clinical Trials Subcommittee of the International Headache Society [34] as it is what patients want [34]. Both from the meta-analyses [9,10] and from the comparative RCT [32] we find that sumatriptan 50 mg has the best efficacy/tolerability ratio. In this choice we have given more weight to the results from the large head-to-head comparative RCT. In addition, over 700 million oral doses of sumatriptan have now been used worldwide (GSK, personal communication). We find that sumatriptan 50 mg is the best candidate triptan for the List of Essential Medicines.

12. Until recently, sumatriptan had the highest cost in all markets where it has been available except in countries where local drug law did not provide patent protection. From earlier this year, with patent expiry, a number of generic products have become available, with substantial reduction in cost. Sumatriptan is now amongst the least expensive of triptans.

The following theoretical pharmacoeconomic example illustrates the cost-effectiveness of a triptan such as sumatriptan 50 mg:

- a. if cost of 1 dose of sumatriptan is 5 USD
- 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 > 20 USD.

15. Proposed text for the WHO Model Formulary:

For acute treatment of migraine:

Aspirin and sumatriptan 50 mg.

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

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