



Triptans-Draft

March 2010

Based on the DERP report of June 2009

Produced by:
The Health Resources Commission
Office for Oregon Health Policy & Research

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Health Resources Commission

The State of Oregon’s Health Resources Commission is a volunteer commission appointed by the Governor. The Health Resources Commission provides a public forum for discussion and development of consensus regarding significant emerging issues related to medical technology. Created by statute in 1991, it consists of four physicians experienced in health research and the evaluation of medical technologies and clinical outcomes; one representative of hospitals; one insurance industry representative; one business representative; one representative of labor organizations; one consumer representative and two pharmacists. All Health Resources Commissioners are selected with conflict of interest guidelines in mind. Any minor conflict of interest is disclosed.

The Commission is charged with conducting medical assessment of selected technologies, including prescription drugs. The commission may use advisory committees or subcommittees, the members to be appointed by the chairperson of the commission subject to approval by a majority of the commission. The appointees have the appropriate expertise to develop a medical technology assessment. Subcommittee meetings and deliberations are public, where public testimony is encouraged. Subcommittee recommendations are presented to the Health Resources Commission in a public forum. The Commission gives strong consideration to the recommendations of the advisory subcommittee meetings and public testimony in developing its final reports.

Overview

The 2001 session of the Oregon Legislature passed Senate Bill 819, authorizing the creation of a Practitioner-managed Prescription Drug Plan (PMPDP). The statute specifically directs the Health Resources Commission (HRC) to advise the Oregon Medical Assistance (OMAP) Department of Human Services (DHS) on this Plan.

In 2007 the Oregon Health Resources Commission (HRC) appointed a pharmaceutical subcommittee to perform evidence-based reviews of pharmaceutical agents. Members of the subcommittee for this review consisted of three Physicians, a Nurse Practitioner, and two pharmacists. All meetings were held in public with appropriate notice provided. The

HRC director worked with the Center for Evidence-based Policy (Center) and the Oregon Health and Science University's (OHSU) Evidence-based Practice Center (EPC) to develop and finalize key questions for this drug class review, specifying patient populations, medications to be studied and outcome measures for analysis, considering both effectiveness and safety. Evidence was specifically sought for subgroups of patients based on race, ethnicity and age, demographics, other medications and co-morbidities. Using standardized methods, the EPC reviewed systematic databases, the medical literature and dossiers submitted by pharmaceutical manufacturers. Inclusion and exclusion criteria were applied to titles and abstracts, and each study was assessed for quality according to predetermined criteria.

The EPC's report, "*Triptans*", June, 2009 was circulated to subcommittee members and posted on the web. The subcommittee met to review the document and this report is the consensus result of those meetings. Time was allotted for public comment, questions and testimony.

This report does not recite or characterize all the evidence that was discussed by the OHSU EPC, the Subcommittee or the HRC. This report is not a substitute for any of the information provided during the subcommittee process, and readers are encouraged to review the source materials. This report is prepared to facilitate the HRC in providing recommendations to the Department of Human Services. The HRC, working together with the EPC, the Center for Evidence Based Policy, DMAP, and the Oregon State University College of Pharmacy, will monitor medical evidence for new developments in this drug class. Approximately twice per year new pharmaceuticals will be reviewed and if appropriate, a recommendation for inclusion in the PMPDP will be made. For pharmaceuticals on the plan, significant new evidence will be assessed and Food and Drug Administration changes in indications and safety recommendations will be evaluated. This report will be updated if indicated. Substantive changes will be brought to the attention of the Health Resources Commission, who may choose to approve the report, or reconvene a subcommittee.

The full OHSU Evidence-based Practice Center's draft report is available via the Office for Oregon Health Policy & Research, Practitioner-Managed Prescription Drug Plan website:

www.oregon.gov/DAS/OHPPR/ORRX/HRC/evidence_based_reports.shtml

Information regarding the Oregon Health Resources Commission and its subcommittee policy and process can be found on the Office for Oregon Health Policy & Research website: <http://www.oregon.gov/DAS/OHPPR/HRC/index.shtml>

You may request more information including copies of the draft report from:

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Information dossiers submitted by pharmaceutical manufacturers are available upon request from the OHSU Center for Evidence-based Policy by contacting:

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There will be a charge for copying and handling in providing documents from both the Office of Oregon Health Policy & Research and the Center for Evidence Based Policy.

Critical Policy

Senate Bill 819

– “The Department of Human Services shall adopt a Practitioner-managed Prescription Drug Plan for the Oregon Health Plan. The purpose of the plan is to ensure that enrollees of the Oregon Health Plan receive the most effective prescription drug available at the best possible price.”

Health Resources Commission

– “Clinical outcomes are the most important indicators of comparative effectiveness”

– “If evidence is insufficient to answer a question, neither a positive nor a negative association can be assumed.”

Clinical Overview

Triptans, also called serotonin 5-hydroxytryptamine (5-HT) receptor agonists, are used to treat migraine and certain other headaches. The cause of migraine is not known.

Scientists have several hypotheses to explain how triptans work.¹

Triptans may be taken subcutaneously, orally as tablets, capsules, or quick-dissolving wafers, or intranasally as a spray. The first triptan, sumatriptan, was introduced in 1991.

Currently, 7 triptans are available in the United States (Table 1). As of June 2003, the original oral tablet form of sumatriptan was replaced by a rapid release tablet (RT®

Technology) that was designed to facilitate early absorption into the bloodstream.

Reformulated sumatriptan was approved as bioequivalent to original sumatriptan based on entire area under the curve (AUC_{0-infinity}) and maximum concentration (C_{max}) and the patent life was not extended. However, in vitro dissolution testing using USP II

apparatus in 0.01 M HCL (aq) at 30 rpm found that at 2 minutes, dispersion rates were nearly 100% for reformulated sumatriptan and less than 20% for original sumatriptan.² In early 2009, the first generic forms of sumatriptan became available on the market.

However, it is not yet clear whether these generic sumatriptan oral tablet products are formulated using RT® Technology or not.

In some cases, patients may treat their migraines using a triptan in combination with other types of pain relievers, such as aspirin or a nonsteroidal anti-inflammatory drug.

The first fixed-dose combination product containing a triptan was introduced in 2008.

This product, called Treximet®, contains sumatriptan 85 mg plus naproxen sodium 500 mg in a single tablet form.

Table 1. Triptans and triptan fixed-dose combination products

Generic name	Brand name	Form and dose (mg)	Black Box Warning?
Almotriptan	Axert®	Oral tablet (6.25 or 12.5)	
Eletriptan	Relpax®	Oral tablet (20 or 40)	
Frovatriptan	Frova®	Oral tablet (2.5)	
Naratriptan	Amerge®	Oral tablet (1 or 2.5)	
Rizatriptan	Maxalt®	Oral tablet (5 or 10)	
	Maxalt-MLT®	Orally disintegrating tablet (5 or 10)	
Sumatriptan	Imitrex®	Oral tablet (25, 50, or 100)	
	Imitrex® Nasal Spray	Nasal spray (5 or 20)	
	Imitrex® Injection, Imitrex StatDose®	Subcutaneous injection (6 or 8)	
Zolmitriptan	Zomig®	Oral tablet (2.5 or 5)	
	Zomig Nasal Spray®	Nasal spray (5)	
	Zomig-ZMT®, Zomig Rapimelt®	Orally disintegrating tableta (2.5 or 5)	
Fixed Dose Combination Products			
Sumatriptan/naproxen	Treximet® ^a	Oral tablet (85/500)	

Drugs for migraine are often classified by whether they are used to prevent migraine attacks (prophylaxis) or to shorten (abort) an attack. All of the triptans available in the United States and Canada are approved for the acute treatment of migraines in adults. None are approved for prophylaxis of migraine or for hemiplegic, ophthalmoplegic, or basilar migraine. Sumatriptan is the only triptan approved in the United States for cluster headache; it is not approved for this indication in Canada.

The clinical efficacy and adverse effects of the different triptans are of considerable interest to researchers and patients, and several review articles³⁻⁸ and meta-analyses⁹⁻¹² have compared them between triptans.

Comparing triptans is complex, however, because of the large variety of outcomes that can be measured in studies. Table 2 lists many of these outcome measures. In most studies, the primary outcome, severity of headache pain after 2 hours, is measured on a 4-point scale (severe, moderate, mild, none). Typically, patients must wait until they have a moderate to severe headache before taking the study medication. Two hours after taking the medication, the patient rates the severity of headache again. A “response” is defined as a reduction in headache from “moderate” or “severe” to “mild” or “none.”

Overdependence on the 2-hour pain-relief measure has been criticized. The main criticism is that a 2-hour response may not be as important to patients as some other measures, such as pain-free response or time to response. Another criticism is that the

change from moderate/severe pain to none/mild may not always be significant. This criticism is based on the premise that a reduction by only 1 point on the scale (for example, from “moderate” to “mild”) may not be associated with important differences in quality of life or function and should not always be counted as a response.¹³

A patient choosing a triptan might consider many other aspects of effectiveness, such as the completeness, speed, and duration of a single response and the consistency of response from headache to headache.¹⁴ Moreover, individual patients may differ in the value they place on each of these attributes of effectiveness and on how they weigh the benefits of treatment against the side effects. For example, suppose that one triptan is more likely to relieve migraine pain within 2 hours, while another is less likely to provide relief but, when it does, it works faster. Or suppose that one triptan is more likely to relieve pain within 2 hours, but more of the patients who experience relief suffer a recurrence of severe pain later in the day. Or suppose that one triptan is more likely to provide headache relief but is also more likely to cause side effects. In each of these situations, the answer to the question “which triptan is better?” may not have a simple answer, or it may have several different answers among patients who have different preferences. For this reason, some experts argue that satisfaction over time may be the best overall measure for comparing triptans.¹⁵ Other experts argue that preference is the best measure:

Quality of the Evidence

For quality of evidence the EPC and subcommittee took into account the number of studies, the total number of patients in each study, the length of the study period and the endpoints of the studies. Statistical significance was an important consideration. The subcommittee utilized the EPC’s ratings of “good, fair or poor” for grading the body of evidence. Overall quality ratings for an individual study were based on the internal and external validity of the trial.

Internal validity of each trial was based on:

- 1) Methods used for randomization
- 2) Allocation concealment and blinding
- 3) Similarity of compared groups at baseline and maintenance of comparable groups
- 4) Adequate reporting of dropouts, attrition, and crossover
- 5) Loss to follow-up
- 6) Use of intention-to-treat analysis

External validity of trials was assessed based on:

- 1) Adequate description of the study population
- 2) Similarity of patients to other populations to whom the intervention would be applied
- 3) Control group receiving comparable treatment
- 4) Funding source that might affect publication bias.

Weighing the Evidence

A particular randomized trial might receive two different ratings: one for efficacy and another for adverse events. The overall strength of evidence for a particular key question reflects the quality, consistency, and power of the body of evidence relevant to that question.

The subcommittee's task was to evaluate

Scope and Key Questions

To identify relevant citations, the EPC searched Ovid MEDLINE® (1996 to week 4 of January 2009), the Cochrane Database of Systematic Reviews® (2nd Quarter 2008), Database of Abstracts of Reviews of Effects (3rd Quarter 2008), and the Cochrane Central Register of Controlled Trials® (3rd Quarter 2008). The EPC attempted to identify additional studies through hand searches of reference lists of included studies and reviews. In addition, the EPC searched the US Food and Drug Administration's Center for Drug Evaluation and Research website for medical and statistical reviews of individual drug products. Finally, the EPC requested dossiers of published and unpublished information from the relevant pharmaceutical companies for this review. The purpose of this review is to compare the triptans for treatment of migraine in adults. The Oregon Evidence-based Practice Center wrote preliminary key questions, identifying the populations, interventions, and outcomes of interest, and based on these, the eligibility criteria for studies. These were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project after considering comments received from the public following posting of a draft version to the Drug Effectiveness Review Project website.

The participating organizations approved the following key questions to guide this review:

Key Questions:

KQ1. How do effectiveness and efficacy outcomes (reduced severity and duration of symptoms, functional outcomes, quality of life, etc) differ for adult patients with migraine within the following treatment comparisons:

- 1a. Monotherapy compared with monotherapy
- 1b. Fixed-dose tablets containing a triptan compared with triptan monotherapy
- 1c. Fixed-dose tablets containing a triptan compared with co-administration of its individual triptan and analgesic components

KQ2. How do the incidence and nature of adverse effects (serious or life-threatening or those that may adversely effect compliance) differ for adult patients with migraine within the following triptan treatment comparisons:

- 2a. Monotherapy compared with monotherapy
- 2b. Fixed-dose tablets containing a triptan compared with triptan monotherapy
- 2c. Fixed-dose tablets containing a triptan compared with co-administration of its individual triptan and analgesic components

KQ3. Are there subgroups of patients based on demographics, other medications, or comorbidities for which one medication or preparation is more effective or associated with fewer adverse effects?

Conclusions:

Limitations of the Evidence:

1. Most of the studies were rated fair quality or below because of variability in endpoints and lack of standard measures for pain relief or time to pain relief.
2. As of June 2003, the original oral tablet form of sumatriptan was replaced by a rapid release tablet (RT® Technology) that was designed to facilitate early absorption into the bloodstream. Reformulated sumatriptan was approved by the FDA as bioequivalent to original sumatriptan
3. None of the head to head trials included in this review utilized the reformulated (rapid release) form of sumitriptan.
4. In early 2009, the first generic forms of sumatriptan became available on the market. However, it is not yet clear whether these generic sumatriptan oral tablet products are formulated using RT® Technology or not.

Conclusions:

1. In comparing the effectiveness and duration of response of different triptans in reducing the severity and duration of symptoms in adult patients with moderate to severe migraine oral almotriptan, eletriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan were similarly efficacious.
2. Good strength evidence for reformulated sumatriptan 85 mg/naproxen 500 mg vs. reformulated sumatriptan 85 mg found the combination superior in pain-free at 2 hours and 24 hours and in normal function, overall productivity, and patient satisfaction. There is no evidence comparing the combination product to an available dose of sumitriptan. There is no evidence comparing the combination product to individual component therapy.
3. There are no fully published head-to-head trials of frovatriptan
4. Nasal sumatriptan and zolmitriptan are effective, but there is insufficient data to determine a clinically significant difference for the comparison of zolmitriptan nasal spray vs. the oral form of the drug. There were no head to head trials comparing sumitriptan nasal spray to the oral form of the drug.
5. Injectable sumatriptan is effective, but there are no acceptable head-to-head studies comparing injectable to the oral form.
6. Injectable and nasal triptans have insufficient evidence to make conclusions about adverse events.
7. Good strength evidence for Almotriptan, eletriptan, naratriptan, rizatriptan oral tablet, rizatriptan orally disintegrating tablet, the conventional tablet form of sumatriptan, zolmitriptan oral tablet, zolmitriptan orally disintegrating tablet, zolmitriptan nasal spray

revealed no differences in overall tolerability and no consistent differences in chest pain/tightness or central nervous system effects.

8. There were either no or poor quality studies for frovatriptan, reformulated sumatriptan, the conventional tablet form of sumatriptan injection and nasal spray.

9. Good strength evidence for reformulated sumatriptan 85 mg/naproxen 500 mg vs. reformulated sumatriptan 85 mg demonstrates no consistent difference in rates of overall adverse events, dizziness, paresthesia, or somnolence.

10. Based on poor strength evidence there is no evidence that any one triptan has a particular advantage or disadvantage over others in any subgroups based on age, gender, race, use of prophylactic treatment, or association with menstruation.

Supporting Evidence:

Key Question 1. How do effectiveness and efficacy outcomes (reduced severity and duration of symptoms, functional outcomes, quality of life, etc) differ for adult patients with migraine?

Key Question 1a. Monotherapy compared with monotherapy

We included 32 head-to-head trials.¹⁹⁻⁵⁰ We found no head-to-head trials involving comparisons with frovatriptan or reformulated sumatriptan.

Most of the head-to-head trials have been previously analyzed in a prior systematic review, the findings of which contrasted with separate meta-analyses of placebo-controlled trials.^{11,12} Additional meta-analyses of indirect comparisons based on placebo-controlled trials of triptans were also identified.^{51,52} Only 1 of these reviews used a set of predefined, explicit criteria (the Jadad score) to assess the internal validity of trials.⁵² The goal of the review was to infer the relative effectiveness of different drugs, including triptans, for the treatment of moderate to severe migraine by using pooled results from placebo-controlled trials. Thus, the authors relied mainly on studies that compared a triptan with a placebo, rather than on direct comparison studies. The investigators selected 5 efficacy measures and 3 adverse effect measures for comparison. Fifty-four trials, most of which were not head-to-head trials, were included in the meta-analysis. The inclusion criteria specified that trials had to be published in peer reviewed journals except for trials of eletriptan, for which unpublished data were obtained directly from the manufacturer.

Ferrari and colleagues used a similar approach but did not consider study quality.^{11,12} The main value of their analysis was that it included the results of all known head-to-head trials, regardless of quality and publication status. Because the analysis was based on original data, the authors were able to calculate the results for endpoints that were not reported in publications, such as the 24-hour response rate. The investigators included 53 clinical trials of triptans, including 12 unpublished trials, all of which were identified by contacting pharmaceutical companies and investigators. Most of the included trials compared a triptan with a placebo, rather than another triptan. Using original data from the manufacturers (except for the trials of frovatriptan), the investigators compared the pooled results for each drug and dosage, using the conventional tablet form of

sumatriptan 100 mg as the reference standard. This meta-analysis was comprehensive, examined important outcome measures, and applied statistical methods appropriately, but the strategy for pooling studies had important weaknesses: The investigators gave equal weight to the results of all studies without considering their quality and pooled recent studies of newer drugs with older ones that were conducted under different circumstances.

Eletriptan

Direct comparisons

We included head-to-head trials that compared eletriptan 40 mg with the encapsulated conventional oral tablet form of sumatriptan 100 mg,²⁴⁻²⁶ encapsulated naratriptan 2.5 mg,²⁸ and encapsulated zolmitriptan 2.5 mg.²⁷

Eletriptan 40 mg compared with the encapsulated conventional tablet form of sumatriptan 100 mg. Three fair-quality trials compared eletriptan 40 mg with the conventional

tablet form of sumatriptan 100 mg.²⁴⁻²⁶ In these studies, sumatriptan was put in a capsule to make it look like eletriptan so that the study could be double-blind. At 2 hours, a significantly greater proportion of patients were pain-free with eletriptan 40 mg than with the encapsulated conventional oral tablet form of sumatriptan 100 mg in 2 of 3 trials.^{24, 26} When we pooled data from all 3 trials, the combined rates were 35% (376/1063) for eletriptan 40 mg and 25% (272/1076) for the encapsulated conventional oral tablet form of sumatriptan 100 mg, with a relative risk of 1.47 (95% CI, 1.11 to 1.94) and a number needed to treat of 10. Two-hour rates of normal function were also significantly greater for eletriptan 40 mg than the encapsulated conventional tablet form of sumatriptan 100 mg in 2 of 3 trials:^{24, 26} 62% (569/913) for eletriptan 40 mg and 56% (457/819) for the encapsulated conventional tablet form of sumatriptan 100 mg, with a relative risk of 1.09 (95% CI, 0.86 to 1.38). We found rates of 24-hour sustained pain-free in only 1 trial, in which eletriptan 40 mg was superior to the encapsulated conventional tablet form of sumatriptan 100 mg (24% compared with 14%; $P < 0.05$).²⁴ When Ferrari and colleagues¹¹ combined these data²⁴ with unpublished data for 24-hour sustained pain-free outcomes from an additional trial,²⁵ the resulting direct difference of -8 (95% CI, -14 to -3) still showed that eletriptan 40 mg was superior to the encapsulated conventional tablet form of sumatriptan 100 mg.

Findings from these trials engendered debate over whether encapsulation of the comparator triptan for blinding purposes suppressed their normal absorption rate and usual effectiveness. This concern has led to multiple studies comparing pharmacokinetic and clinical effects of the conventional tablet form of sumatriptan tablets with and without encapsulation.

In vitro and in vivo dissolution testing by the manufacturers of eletriptan and the conventional tablet form of sumatriptan have produced conflicting results.⁵³⁻⁵⁵ In an in vitro dissolution study funded by the manufacturer of eletriptan,⁵⁴ no significant difference in dissolution rate (estimated as area under the curve) was found for the conventional tablet form of sumatriptan 100 mg, with or without encapsulation based on the ratio of geometric means of 0.99 (90% CI, 0.92 to 1.06). However, an in vivo study (Fuseau 2001), funded by the manufacturer of the conventional tablet form of sumatriptan, showed absorption was delayed between 0 to 2 hours after dosing (AUC2)

when the conventional tablet form of sumatriptan 50 mg was encapsulated compared to when it was not encapsulated in a sample of 26 healthy adults (geometric mean treatment ratio 0.79; 90% CI, 0.59 to 1.05) and in a sample of 30 adults during a migraine (n=30) (geometric mean treatment ratio 0.73; 90% CI, 0.52 to 1.02).⁵⁵ The Fuseau trial has been criticized by an investigator sponsored by the manufacturer of eletriptan for using twice as much magnesium stearate to encapsulate sumatriptan than was used in the original head-to-head trials of eletriptan and suggested that the greater quantity magnesium stearate could have hampered capsule dissolution and confounded absorption. Also, it is unclear why the Fuseau and colleagues evaluated only the 50 mg dose of the conventional tablet form of sumatriptan and not also the 100 mg dose or why they used a 90% confidence interval to evaluate statistical significance, rather than the more common and more stringent 95% confidence interval.

Subsequently, in another study funded by the manufacturer of eletriptan involving 10 healthy volunteers, the conventional tablet form of sumatriptan 100 mg and encapsulated sumatriptan 100 mg were found to be similar in elapsed time to initial capsule disintegration (6 minutes compared with 5 minutes) and in mean time to complete disintegration (18 ± 14 minutes compared with 16 ± 7 minutes).⁵³

Meta-analyses have also been conducted to compare the 2-hour pain relief and pain-free outcomes from head-to-head trials of eletriptan and the encapsulated conventional tablet form of sumatriptan to those from all other trials of either eletriptan or the unencapsulated conventional tablet form of sumatriptan, respectively.^{11, 56, 57} But, none has conclusively found that the clinical efficacy of the conventional oral tablet form of sumatriptan 100 mg on 2-hour pain-relief or painfree outcomes was significantly decreased in trials where it was encapsulated compared with trials where it was not encapsulated.

In their 2002 meta-analysis,¹¹ Ferrari and colleagues conducted a sensitivity analysis to examine how company sponsorship may have influenced results for sumatriptan and placebo comparators.¹¹ Because the eletriptan-encapsulated sumatriptan comparator trials were all conducted by Pfizer,²⁴⁻²⁶ this provided an opportunity for qualitative indirect comparison of average absolute 2-hour pain-free rate for the conventional tablet form of sumatriptan 100 mg with and without encapsulation. For the outcome of 2-hour pain-free, the *overall* average absolute rate for sumatriptan 100 mg was 29% (95% CI, 27 to 31) and was 8% (95% CI, 7 to 9) for placebo. In the Pfizer-conducted eletriptan-sumatriptan comparator trials, however, Ferrari and colleagues found lower average absolute 2-hour pain-free rates for encapsulated sumatriptan 100 mg and for placebo, respectively.

Although inconclusive, the findings of Ferrari and colleagues suggest the presence of heterogeneity between Pfizer-conducted and other company conducted trials that could have influenced 2-hour pain-free results. However, because the pattern of non-encapsulated placebo was similar to that of encapsulated sumatriptan – lower efficacy in Pfizer-conducted trials – use of encapsulation for blinding could not be the only source of heterogeneity in these trials.

One meta-analysis compared the time course of response for the conventional tablet form of sumatriptan with and without encapsulation using model-based random-effects logistic regression techniques and data from 19 head-to-head and placebo-controlled trials.⁵⁶ No significant difference was found at any time point between 0 and 4 hours in proportion of patients who achieved pain relief for the conventional tablet form of sumatriptan with or without encapsulation.

In 2005, we conducted our own meta-analysis to compare the mean absolute rates of 2-hour pain relief and pain-free for eletriptan and the conventional tablet form of sumatriptan. We compared data from head-to-head trials of eletriptan 40 mg and the encapsulated conventional tablet form of sumatriptan 100 mg²⁴⁻²⁶ with data from all other available head-to-head trials and placebo-controlled trials involving either triptan. For the conventional tablet form of sumatriptan 100 mg, the mean rates of 2-hour pain relief and pain-free were numerically *lower* when it was encapsulated compared to when it was not encapsulated, but overlapping confidence intervals suggest that the difference is not statistically significant. Unexpectedly, however, for eletriptan 40 mg, the mean rate of 2-hour pain relief and pain-free were numerically *higher* in trials where the comparator was the encapsulated conventional tablet form of sumatriptan compared to when the comparator was placebo or another unencapsulated triptan. But, here again, overlapping 95% confidence intervals suggest that the difference is not statistically significant. Overall, meta-analyses have provided suggestive evidence that sumatriptan's usual efficacy was suppressed when it was encapsulated for blinding purposes in the Pfizer-conducted trials. However, because the pattern of lower efficacy was also seen for non-encapsulated placebo and a pattern of higher efficacy was seen for non-encapsulated eletriptan, our (EPC) conclusion is that use of encapsulation cannot provide the entire explanation for the unexpected results in the Pfizer-conducted eletriptan-sumatriptan comparator trials. Therefore, using meta-regression techniques, the EPC explored the impact of potential sources of clinical heterogeneity including mean age, percentage of female subjects, and percentage with severe baseline pain. However, even after adjustment for those patient variables, the EPC found that the modest differences persisted between 2-hour pain-relief and pain-free outcomes in the trials of eletriptan and the encapsulated conventional tablet form of sumatriptan 100 mg compared with those in other trials of either eletriptan or nonencapsulated sumatriptan. Other variables of interest were recruitment method, type of run-in period, type of prior migraine treatment, including whether the trial population had been previously exposed to triptans, and year the study was conducted, but the publications provided insufficient data to assess their effects. Other variables, such as the scientific group conducting the study, place of study, and sponsorship might contribute to the difference, but they are confounded with the effects of drug and were not included in the analysis.

We (EPC) also explored the presence of unexplained post-randomization exclusions of treated patients as another possible explanation for the unexpected findings in the 3 head-to-head trials of eletriptan compared with the encapsulated conventional tablet form of sumatriptan 100 mg.²⁴⁻²⁶ As in the majority of trials of triptans, the head-to-head trials of eletriptan and the encapsulated conventional tablet form of sumatriptan 100 mg excluded from their efficacy analyses an average of 16% of randomized patients who took no study medication for the primary reason that they did not have a treatable migraine during the study period. However, unlike in most other trials, an additional subset (mean=7%, range=5% to 12%) of *treated* patients who were not "evaluable" due to unspecified violations of the protocol were excluded from the 2-hour efficacy analyses in the head-to-head trials of eletriptan compared to the encapsulated conventional tablet form of sumatriptan 100 mg.²⁴⁻²⁶

Using a "worst-case scenario" approach, the EPC estimated pooled 2-hour pain-free rates for the *all-treated* populations which we compared for eletriptan and the encapsulated

conventional tablet form of sumatriptan 100 mg based on both risk difference and relative risk meta-analyses using random-effects models. All treated patients excluded from the eletriptan 40 mg groups were included in the “worst-case scenario” analyses as treatment failures and all treated patients excluded from the encapsulated conventional tablet form of sumatriptan 100 mg groups were included as if they achieved 2-hour pain-free outcomes. In contrast to published findings based on the “evaluable” populations, in our worst-case scenario analyses, the difference in rates of 2-hour pain-free between eletriptan and the encapsulated conventional tablet form of sumatriptan 100 mg was smaller and was no longer statistically significant.

It is important to note that results from our “worst-case scenario” analysis are hypothetical and, without knowledge of the real reasons for the exclusion of the treated patients, it is not possible for us to assess whether such bias exists or to what degree. Therefore, meaningful interpretation of results from the head-to-head trials of eletriptan compared with the encapsulated conventional tablet form of sumatriptan 100 mg is still not possible.

Eletriptan 40 mg compared with encapsulated naratriptan 2.5 mg. We included 1 fair quality trial of 483 adults that treated moderate to severe migraines and found eletriptan 40 mg to be superior to encapsulated naratriptan 2.5 mg in rates of 2-hour pain-free (35% compared with 14%; $P < 0.001$), 2-hour normal function (60% compared with 52%; $P = 0.014$), and 24-hour sustained pain-free (22% compared with 11%; $P < 0.05$).²⁸

Eletriptan 40 mg compared with encapsulated zolmitriptan 2.5 mg. We included 1 fair quality trial of 1337 adults that treated moderate to severe migraines and found eletriptan 40 mg to be similar to the lowest recommended dosage of zolmitriptan 2.5 mg (encapsulated) on rates of 2-hour pain-free (32% compared with 26%), 2-hour functional response (61% compared with 55%), and 24-hour sustained pain-free (20% compared with 17%).²⁷

Placebo-controlled trials: Eletriptan

Placebo-controlled trials provided supplemental information about the efficacy of eletriptan 40 mg in the early treatment of mild migraines and improving quality of life.

Early intervention. The efficacy of eletriptan 40 mg administered while pain is mild has been demonstrated in 1 fair-quality placebo-controlled trial of 565 adults.⁵⁸ In this trial, patients were instructed to take trial medication as soon as they were sure that they were experiencing a migraine. Despite being encouraged to take the medication while the pain was still mild, almost half of patients reported pain that was moderate to severe upon treatment. Consequently, the investigators based analyses on only the subgroup of patients whose pain was still mild at baseline. In this subgroup, eletriptan 40 mg was superior to placebo in rates of 2-hour pain-free (68% compared with 25%; $P < 0.0001$) and 24-hour sustained pain-free (56% compared with 18%; $P < 0.01$). Based on our independent random-effects meta-analysis for 2-hour pain-free, the relative risk was 2.72 (95% CI, 1.92 to 3.84) and the number-needed-to-treat was 2. For 24-hour pain-free, the relative risk was 3.21 (95% CI, 2.09 to 4.94) and the number needed-to-treat was 3.

Work productivity. We included 2 placebo-controlled trials that evaluated the efficacy of eletriptan 40 mg in improving work productivity outcomes.^{59, 60} Eletriptan 40 mg reduced total time lost (4 compared with 9 hours; P not reported) and work time lost (2.5

compared with 4 hours; $P=0.013$) in 1 placebo-controlled trial.⁶⁰ In the other trial, improvements on the Work Productivity Questionnaire (PQ-7) were significantly greater for eletriptan 40 mg than placebo (+22.4 compared with +11.8; $P<0.01$).⁵⁹

Rizatriptan

Direct comparisons

Rizatriptan 10 mg compared with the conventional tablet form of sumatriptan.

We included 4 fair-quality head-to-head trials comparing rizatriptan 10 mg with the conventional tablet form of sumatriptan 100 mg^{36, 37} and the conventional tablet form of sumatriptan 50 mg in patients with migraine of moderate to severe pain intensity.^{32, 33} Supplemental unpublished data for 3 of these trials was provided by the manufacturer.^{32, 33, 36} In terms of quality, the main limitation for both trials of rizatriptan 10 mg compared with the conventional tablet form of sumatriptan 100 mg was a randomization process that did not achieve balance between treatment groups on all baseline characteristics. In the trial conducted by Tfelt-Hansen and colleagues, patients in the rizatriptan 10 mg group were significantly younger than patients in the conventional tablet form of sumatriptan 100 mg group (37 years compared with 39 years; $P<0.01$). The age difference was adjusted for in the analysis of the primary outcome of time to pain relief, but not for other outcomes.³⁶ In the trial by Visser and colleagues, patients in the conventional tablet form of sumatriptan 100 mg group were predominantly from tertiary referral centers in the Netherlands, and 62% had severe pain at baseline. In contrast, the rizatriptan 10 mg, 20 mg, and 30 mg and placebo groups consisted of patients from the Netherlands and the United States, with 47% to 51% having severe pain at baseline. The difference in proportion of patients with severe pain at baseline was statistically significant for only the comparison of the conventional tablet form of sumatriptan 100 mg (62%) with placebo (47%; P not reported).³⁷

Findings were mixed across these trials and do not demonstrate a clear advantage for rizatriptan over the conventional tablet form of sumatriptan 50 mg or 100 mg. Findings were most favorable for rizatriptan 10 mg over the conventional tablet form of sumatriptan 100 mg in the Tfelt-Hansen trial, which involved 1099 adults with migraine pain of moderate to severe intensity.³⁶ However, this trial differed from the others in one main way: Patients with prior exposure to rizatriptan were excluded, which limits the applicability of these findings to patients who are rizatriptan-naïve. In the other 3 trials, patients were enrolled regardless of prior triptan use.^{32, 33, 37}

At 1 hour, rates of pain-free were generally higher in the rizatriptan 10 mg treatment groups, but only 1 difference in 1 trial reached statistical significance, a comparison with the conventional tablet form of sumatriptan 50 mg.³² At 2 hours, rates of pain-free and normal function were again generally higher in the rizatriptan 10 mg treatment groups, but the differences reached statistical significance only in the Tfelt-Hansen trial.³⁶

For the comparison of the conventional tablet form of sumatriptan 100 mg to rizatriptan 10 mg, although the difference in 2-hour pain-free reached statistical significance in only 1³⁶ of 2 individual trials,^{36, 37} when Ferrari and colleagues¹¹ pooled these trials' data, the combined direct difference (-7) was statistically significant (95% CI, -13 to -1). For the comparison of the conventional tablet form of sumatriptan 50 mg to rizatriptan, even when Ferrari and colleagues pooled data from the 2 individual trials, the combined direct

difference (-3) did not reach statistical significance for 2-hour pain-free outcomes (95% CI, -9 to +2).¹¹

At 24 hours, the rate of recurrence was similar for rizatriptan 10 mg and the conventional tablet form of sumatriptan 50 mg³² and 100 mg.^{36, 37} Data on sustained pain-free outcomes at 24 hours were not reported in the original publications. However, based on pooled direct difference estimates for 24-hour sustained pain-free outcomes that were calculated by Ferrari and colleagues using unpublished data obtained from the drugs' manufacturers, differences between rizatriptan 10 mg and the conventional tablet form of sumatriptan 50 mg (-2; 95% CI, -7 to +3) and 100 mg (-4; 95% CI, -9 to +2) were not statistically significant.¹¹ For 24-hour quality of life, there were generally no significant differences in mean scores for the 5 domains of the Migraine-Specific Quality-of-Life Questionnaire across the trials comparing rizatriptan 10 mg with the conventional tablet form of sumatriptan 50 mg^{32, 33} or 100 mg.³⁶ The only exception was that the mean score on the Work Functioning domain was significantly greater for rizatriptan 10 mg than the conventional tablet form of sumatriptan 50 mg (12.9 compared with 12.3; $P=0.029$) in 1 of the 2 trials.³² Quality-of-life outcomes were not reported in the Visser trial of rizatriptan 10 mg and the conventional tablet form of sumatriptan 100 mg.

Rizatriptan 10 mg compared with naratriptan 2.5 mg.

Rizatriptan 10 mg was superior to naratriptan 2.5 mg in 1 good-quality trial (N=522).³¹ However, limitations in consistency and applicability reduced the strength of the findings from this trial. Rizatriptan 10 mg was superior to naratriptan 2.5 mg on the 2-hour outcomes of time to pain relief (hazard ratio 1.62; 95% CI, 1.26 to 2.09), rates of pain-free (45% compared with 21%; $P=0.001$), and normal functioning (39% compared with 23%; $P<0.001$). At 2-hours, overall satisfaction was also measured using a 7-point scale (1=completely satisfied and 7=completely dissatisfied) and was significantly higher for rizatriptan 10 mg (3.55; $P<0.001$) than naratriptan 2.5 mg (4.21). But, inconsistent with 2-hour outcomes, differences between rizatriptan 10 mg and naratriptan 2.5 mg were not statistically significant on 24-hour outcomes. At 24 hours, similar numbers of patients on rizatriptan 10 mg and naratriptan 2.5 needed additional medication (40% compared with 46%; P not reported), had recurrences (33% compared with 21%; P not reported), and had improved scores on the Migraine-Specific Quality-of-Life Questionnaire (P not reported), including Work Functioning (11.73 compared with 11.86), Social Functioning (12.16 compared with 11.92), Energy/Vitality (11.56 compared with 11.95), Migraine Symptoms (12.42 compared with 12.37), and Feelings/Concerns (11.55 compared with 11.79).⁶¹ Additionally, the applicability of this trial was potentially limited due to its exclusion of patients with prior exposure to rizatriptan or naratriptan.

Rizatriptan 10 mg compared with zolmitriptan 2.5 mg.

Rizatriptan 10 mg showed an advantage over the lowest recommended dose of zolmitriptan 2.5 mg on 2-hour outcomes in a fair-quality trial of 766 adults with moderate to severe migraine pain.³⁵ Patients were eligible for enrollment regardless of their prior triptan use, but only 30% had used any triptan within the past 30 days. Compared with zolmitriptan 2.5 mg, rizatriptan had a similar rate of 1-hour pain-free (13% compared with 10%) and superior rates of 2-hour pain-free (43% compared with 36%; $P<0.05$) and normal function (45% compared with 37%; $P<0.05$). At 24 hours, rizatriptan 10 mg and

zolmitriptan 2.5 mg had similar rates of recurrence (28% compared with 29%) and similar mean scores on all 5 domains of the Migraine-Specific Quality-of-Life Questionnaire.

Placebo-controlled trials: Rizatriptan

Because head-to-head trials involving rizatriptan lacked data about consistency of effect and early treatment of migraine, we examined placebo-controlled trials that measured these outcomes.

Consistency. We found 1 fair-quality placebo-controlled trial that examined the use of rizatriptan 10 mg for treatment of 4 consecutive migraine headaches.⁶² Rizatriptan showed consistently higher 2-hour response rates than placebo during headache 1 (77% [320/246] compared with 37% [30/82]; $P < 0.01$), headache 2 (78% [228/291] compared with 37% [27/73]; P not reported), headache 3 (80% [207/259] compared with 28% [21/75]; P not reported), and headache 4 (74% [190/255] compared with 54% [31/57]; P not reported). However, it is unclear whether differences between rizatriptan and placebo groups in the number of patients excluded from the analyses of headache 2 (9% compared with 11%), headache 3 (19% compared with 8%), and headache 4 (20% compared with 30%) may have resulted in groups compared after headache 1 being dissimilar in important patient characteristics that could have biased the analyses.

Early intervention.

The efficacy of rizatriptan 10 mg administered early in a migraine, while pain is mild, has been demonstrated in 2 identically designed, good-quality placebo controlled trials named Rizatriptan TAME1 (Treat A Migraine Early) and TAME2.⁶³ Findings from TAME1 and TAME2 were both reported in a single publication. Eligibility criteria required a history of migraines that typically started out mild. The study plan was for patients to treat their migraines while still mild in severity and present for less than 1 hour, but not spontaneously resolving. In both trials, rizatriptan was superior to placebo in rates of 2-hour pain-free and 24-hour sustained pain-free. Rates of 2-hour pain-free for rizatriptan compared with placebo in TAME1 were 57% and 31%, respectively, and in TAME2 were 59% and 31%, respectively (P not reported for pairwise comparisons). Rates of 24-hour sustained pain-free for rizatriptan compared with placebo in TAME1 were 43% and 23%, respectively, and in TAME2 were 48% and 25%, respectively (P not reported for pairwise comparisons). Based on our (EPC) independent random-effects meta-analysis, these findings resulted in a pooled relative risk of 1.86 (95% CI, 1.57 to 2.21) and a number-needed-to-treat of 3 for 2-hour pain-free outcomes. For 24-hour sustained pain-free rates, we calculated a pooled relative risk of 3.52 (95% CI, 1.67 to 7.42) and a number-needed-to-treat of 5.

Rizatriptan orally disintegrating tablets

Direct comparisons

Rizatriptan orally disintegrating tablet 10 mg compared with the conventional tablet form of sumatriptan 100 mg.

We found no head-to-head trials that compared rizatriptan orally disintegrating tablet 10 mg to sumatriptan 100 mg; that evaluated quality-of-life, workplace, or consistency outcomes; or that evaluated early treatment of mild migraine. Two open, fair-quality trials demonstrated rizatriptan orally disintegrating tablet 10 mg to be superior to the

conventional tablet form of sumatriptan 50 mg on preference and rates of 2-hour normal function and pain-free.^{39, 41} Similar numbers of patients had recurrence of migraine within 24-hours with both rizatriptan orally disintegrating tablet 10 mg and the conventional tablet form of sumatriptan 50 mg. Only 1 of the 2 trials reported 24-hour sustained pain-free outcomes, and the rate was significantly greater for rizatriptan orally disintegrating tablet 10 mg than the conventional tablet form of sumatriptan 50 mg (41% compared with 32.3%; odds ratio 1.47; 95% CI, 1.14 to 1.90).⁴¹

Rizatriptan orally disintegrating tablet 10 mg compared with eletriptan 40 mg.

We also found 1 fair-quality, open head-to-head trial primarily designed to evaluate preference for rizatriptan orally disintegrating tablet 10 mg compared with eletriptan 40 mg in 439 adults who had no prior experience with either triptan.³⁸ Greater numbers of patients expressed a preference for treatment with rizatriptan orally disintegrating tablet 10 mg (61%; 95% CI, 56 to 66) than eletriptan 40 mg (39%; 95% CI, 34 to 44), with the most common reason being “relieved my headache pain faster.” At 2 hours, similar numbers of patients in the rizatriptan and eletriptan groups were completely or very satisfied with study medication (45% compared with 40%), were pain-free (52% compared with 50%), or had any functional disability (43% compared with 47%). Rates of 24-hour sustained pain-free were also similar for rizatriptan orally disintegrating tablet 10 mg (43%) and for eletriptan 40 mg (47%).

Placebo-controlled trials: Rizatriptan orally disintegrating tablet

We did not find any placebo-controlled trials that evaluated rizatriptan orally disintegrating tablet 10 mg for consistency over multiple attacks. We are aware of a placebo-controlled trial of rizatriptan orally disintegrating tablet 10 mg for early treatment of migraine (N=207), for which an in-press article is pending publication in an upcoming issue of *Headache*. However, it was brought to our attention after our search end date of January 2009 and, consequently, a review of its findings will be postponed until the next update of this review.

Although we did not find any published quality-of-life data, the manufacturer provided unpublished data⁶¹ for 1 published placebo-controlled trial.⁶⁴ This trial involved treatment of 555 adults with moderate to severe pain intensity and prior triptan use was allowed. The Migraine-Specific Quality-of-Life Questionnaire was used to measure quality of life at 24 hours; rizatriptan orally disintegrating tablet 10 mg was superior to placebo ($P < 0.001$) in mean scores on all 5 domains: Migraine Symptoms (12.6 compared with 10.3), Feelings/Concerns (11.2 compared with 8.6), Work Functioning (12.6 compared with 10.5), Social Functioning (12.2 compared with 10.1), and Energy/Vitality (11.6 compared with 9.6).

Zolmitriptan: Oral tablet, orally disintegrating tablet, nasal spray

Direct comparisons: Oral tablet

We included head-to-head trials of oral zolmitriptan 5 mg compared with the conventional tablet form of sumatriptan 100 mg⁴⁵ and 50 mg.^{44, 46} We also identified unpublished data from a trial comparing zolmitriptan 2.5 mg with naratriptan 2.5 mg (Protocol 311CIL/0099) that was accessed in the form of a summary report on the manufacturer’s website (<http://www.astrazenecaclinicaltrials.com>). The trials involving

the conventional tablet form of sumatriptan^{12, 65} and naratriptan 2.5 mg⁶⁵ have been previously evaluated in meta-analyses that estimated direct differences and rate ratios. All 3 trials involved treatment of moderate to severe migraines. The trials comparing zolmitriptan 5 mg with the conventional tablet form of sumatriptan 50 mg provided data on consistency of treatment across 6 consecutive headaches.^{44,45} We found no head-to-head trials involving zolmitriptan that evaluated its effects in early treatment of mild migraines or its effects on quality of life or work productivity.

Zolmitriptan 5 mg compared with the conventional tablet form of sumatriptan.

One fair quality trial compared zolmitriptan 5 mg to the conventional tablet form of sumatriptan 100 mg in 1058 adults who had never been treated with either triptan.⁴⁵ Zolmitriptan 5 mg and the conventional tablet form of sumatriptan 100 mg had similar rates of pain-free at 1 hour (8% compared with 10%; rate ratio 0.70; 95% CI, 0.47 to 1.04)⁶⁵ and 2 hours (29% compared with 30%; rate ratio 0.98; 95% CI, 0.81 to 1.18),⁶⁵ no activity impairment at 2 hours (data not reported), recurrence at 24 hours (26% compared with 28%), and complete response at 24 hours (39% compared with 38%). In the Ferrari meta-analysis of unpublished data provided by manufacturers, the conventional tablet form of sumatriptan 100 mg and zolmitriptan 5 mg also had similar rates of 24-hour pain-free (direct difference -1; 95% CI, -5 to +6).¹² For the comparison of zolmitriptan 5 mg to the conventional tablet form of sumatriptan 50 mg, 2-hour and 24-hour pain-free rates were published for only 1 of the 2 trials for 1522 (90%) of participants who treated at least 2 attacks.⁴⁶ Using those data and unpublished data for the other trial,⁴⁴ Ferrari and colleagues calculated pooled direct differences for 2-hour pain-free (0%; 95% CI, -4 to +4) and 24-hour sustained pain-free (-1%; 95% CI, -5 to +3), suggesting that zolmitriptan 5 mg and the conventional tablet form of sumatriptan 50 mg have similar effects on these outcomes.¹²

The 2 head-to-head trials comparing zolmitriptan 5 mg to the conventional tablet form of sumatriptan 50 mg also provided the best data on consistency. The first of these, conducted in the United States, compared zolmitriptan 2.5 mg and 5 mg to sumatriptan 25 mg and 50 mg.^{44, 66} Over 6 months, each patient was treated for up to 6 consecutive headaches. Patients were recruited from primary care, neurology, and research clinics. Of 1445 patients enrolled, 1212 treated at least 2 migraine headaches and 1043 completed the study. However, this trial has been criticized because it did not exclude patients who had previously taken sumatriptan.⁶⁷ There may have been a selection bias favoring zolmitriptan, since patients who responded inconsistently to sumatriptan in the past may be more likely to enroll in an experimental trial of a newer triptan. To assess consistency, the authors calculated the proportion of patients who responded in 2 hours in 80% to 100% of headaches. The results indicate that the 2-hour response is not a reliable indicator of consistency across multiple migraine headaches.

A good-quality trial of similar design was conducted in Europe.⁴⁶ In that trial, there were essentially no differences in efficacy among zolmitriptan 2.5 mg, zolmitriptan 5 mg, and sumatriptan 50 mg. The 3 treatments also had similar consistency across attacks: about 40% of patients in each group reported a 2-hour response in 80% or more of their headaches.

Zolmitriptan 2.5 mg compared with naratriptan 2.5 mg.

An unpublished trial comparing zolmitriptan 2.5 mg with naratriptan 2.5 mg consisted of 2 parts. In Part 1, 553 adults were randomized to treat 1 headache with zolmitriptan 2.5 mg, naratriptan 2.5 mg, or placebo. The 438 who treated a headache and provided efficacy data were re-randomized to either zolmitriptan 2.5 mg or naratriptan to treat up to 3 more headaches in Part 2. According to the trial's brief summary report, a higher proportion of patients in the zolmitriptan groups had headaches of severe intensity at baseline in both Parts 1 and 2. However, we could not examine the magnitude of these differences or any other baseline characteristics as their details were not provided in the trial summary report. It was noted that the baseline difference was more marked in Part 1 and was adjusted for in the analysis of 2-hour pain-relief data. The adjusted 2-hour pain-relief rate was similar for zolmitriptan 2.5 mg and naratriptan 2.5 mg (54% compared with 47%). Although the trial summary did not report 2-hour or 24-hour pain-free outcomes, Chen and colleagues obtained these data from the manufacturer and estimated risk ratios of 1.73 (95% CI, 1.10 to 2.72) and 1.04 (95% CI, 0.74 to 1.47), respectively.⁶⁵ However, as these risk ratios do not appear to have been adjusted for the above-described baseline differences in headache intensity, we interpret these risk ratios with caution.

Direct comparisons: Zolmitriptan orally disintegrating tablets and nasal spray

We included 1 head-to-head trial comparing zolmitriptan orally disintegrating tablet 2.5 mg with the conventional tablet form of sumatriptan 50 mg⁴⁹ (however it was rated poor quality and will not be discussed) and 2 head-to-head trials that compared different formulations of zolmitriptan.^{47, 48}

Comparisons of different zolmitriptan formulations. One good-quality, randomized trial (N=1372) compared double-blinded, double-dummy treatment with zolmitriptan nasal spray 0.5 mg, 1.0 mg, 2.5 mg, and 5.0 mg and oral zolmitriptan 2.5 mg.⁴⁷ Another trial used a crossover design to compare patient preference among zolmitriptan orally disintegrating tablet 2.5 mg, zolmitriptan standard oral tablet 2.5 mg, and zolmitriptan nasal spray 5 mg, but it was rated poor quality due to lack of blinding, presence of high attrition, and lack of separately reported results from the first treatment period.⁴⁸

The good-quality trial found zolmitriptan nasal spray 5 mg to be superior to zolmitriptan standard oral tablet 2.5 mg on rate of pain-free at 30 minutes (7% compared with 2%; $P<0.05$) and 45 minutes (10% compared with 5%; $P<0.05$) and on rate of resumption of normal activities at all time points (53% compared with 45%; P not reported).

Zolmitriptan nasal spray 5 mg and zolmitriptan standard oral tablet 2.5 mg were similar on rate of 2-hour pain-free (38% compared with 37%) and rate of recurrence at 24 hours (26% for both). Zolmitriptan nasal spray 2.5 mg was similar to zolmitriptan standard oral tablet 2.5 mg in rate of pain-free at timepoints between 30 minutes and 1 hour, but was inferior at 2 hours (26% compared with 37%; $P<0.05$) and 4 hours (43% compared with 54%; $P<0.05$).

Placebo-controlled trials: Zolmitriptan

Early intervention.

The efficacy of zolmitriptan standard oral tablet 2.5 mg administered while pain is mild has been demonstrated in 1 fair-quality placebo-controlled trial.⁶⁸ In this trial, 280 patients were instructed to administer treatment when pain was still mild and within 4 hours of onset. Zolmitriptan was superior to placebo in rates of 2-hour pain-free (43% compared with 18%; $P<0.001$) and 2-hour normal function (68% compared with 51%; $P<0.01$). The only 24-hour outcome reported was need for further medication, which was

significantly lower after zolmitriptan 2.5 mg (46%) than placebo (71%; $P < 0.0001$). Based on our independent random effects meta-analysis, these findings correspond to a pooled relative risk of 2.⁴¹ (95% CI, 1.81 to 3.20) and a number-needed-to-treat of 4 for 2-hour pain-free outcomes.

Almotriptan

Direct comparisons

We included 4 head-to-head trials of almotriptan 12.5 mg, including comparisons to the conventional tablet form of sumatriptan 100 mg²⁰ and 50 mg,⁶⁹ rizatriptan 10 mg,²² and zolmitriptan 2.5 mg.²³ Three^{21, 23, 69} of 4 head-to-head trials were previously evaluated in a recent meta-analysis.⁷⁰

Almotriptan 12.5 mg compared with the conventional tablet form of sumatriptan.

Both trials comparing almotriptan 12.5 mg with the conventional tablet form of sumatriptan were rated fair quality due to differences between comparison groups at baseline, and both provided data on 2-hour pain-free and 24-hour recurrence outcomes.^{20, 69} Rate of 2-hour pain-free was consistently lower for almotriptan 12.5 mg in both trials. Compared with the conventional tablet form of sumatriptan 50 mg (25%), significantly fewer patients were pain-free at 2 hours after taking almotriptan 12.5 mg (18%; $P = 0.005$). It is unknown, however, whether the higher mean body weight in the almotriptan group (74.5 kg compared with 72.3 kg; $P = 0.003$) may have disadvantaged those patients' treatment response. Compared with the conventional tablet form of sumatriptan 100 mg, fewer patients on almotriptan 12.5 mg were pain-free at 2 hours (28% compared with 33%), but this difference was not statistically significant.²⁰ At 24 hours, rates of recurrence for almotriptan 12.5 mg were slightly higher than for the conventional tablet form of sumatriptan 50 mg (27% compared with 24%)⁶⁹ and slightly lower than for the conventional tablet form of sumatriptan 100 mg (18% compared with 25%).²⁰ Differences in 24-hour recurrence rates were nonsignificant in both trials. Sustained 24-hour pain-free, functional disability, and quality-of-life outcomes were not reported in either of the original trials comparing almotriptan 12.5 mg with the conventional tablet form of sumatriptan. Based on findings from a more recent review of almotriptan trials, however,⁷⁰ similar rates of patients had sustained 24-hour pain-free outcomes with almotriptan 12.5 mg and the conventional tablet form of sumatriptan 100 mg (rate ratio 0.86; 95% CI, 0.62 to 1.21).

Almotriptan 12.5 mg compared with zolmitriptan 2.5 mg.

One good-quality trial provided evidence that almotriptan 12.5 and zolmitriptan 2.5 mg were similar on 2-hour and 24-hour efficacy outcomes in patients who were enrolled regardless of prior triptan use.²³ Both almotriptan and zolmitriptan tablets were encapsulated for blinding purposes. At 2-hours, almotriptan 12.5 mg and zolmitriptan 2.5 mg were similar in rates of pain-free (43% compared with 48%) and no functional impairment (47% compared with 49%). Almotriptan 12.5 mg and zolmitriptan 2.5 mg were also similar in rates of "excellent" satisfaction (16% compared with 15%) and 24-hour sustained pain-free plus no adverse events (29% compared with 32%).

Almotriptan 12.5 mg compared with rizatriptan 10 mg.

One fair-quality trial was designed primarily to compare patient preference for open almotriptan 12.5 mg against open rizatriptan 10 mg in patients from Germany, Italy, and Spain who had never been treated with either triptan.²² Among the 255 of 327 patients in the 2-attack intention-to-treat population who recorded a preference for one triptan over another, half preferred almotriptan (n=128) and the other half preferred rizatriptan (n=127). Among the secondary efficacy variables analyzed (e.g., 2-hour pain-free; 2-hour pain-relief; sustained pain-free; sustained pain-free plus no adverse events; use of rescue medications; recurrence between 2-24 hours; recurrence between 24-48 hours), the only significant difference found indicated an advantage for rizatriptan 10 mg over almotriptan 12.5 mg on 2-hour pain-free outcomes (58% compared with 52%; $P=0.03$). This trial did not report quality-of-life or functional disability outcomes.

Placebo-controlled trials: Almotriptan

As 24-hour pain-free outcomes were not reported in head-to-head trials of almotriptan 12.5 compared with conventional sumatriptan 100 mg, we relied on findings from the meta-analysis by Ferrari and colleagues that used data from placebo-controlled trials to enable indirect comparison between the 2 triptans.¹¹ We also included placebo-controlled trials of almotriptan that analyzed consistent treatment across multiple headaches⁷¹ and early treatment of mild migraine.⁷²⁻⁷⁴

Indirect comparison of almotriptan with the conventional tablet form of sumatriptan 100 mg for 24-hour pain-free.

In their meta-analysis of 53 triptan trials, Ferrari and colleagues included data from 3 abstracts of placebo-controlled trials of almotriptan 12.5 mg.⁷⁵⁻⁷⁷ Using pooled data from the almotriptan 12.5 arms of these trials, they calculated a mean absolute rate of sustained pain-free, which they compared to the mean for the conventional tablet form of sumatriptan. The actual mean value and 95% confidence interval was not provided for almotriptan but it was described as being higher than for the conventional tablet form of sumatriptan 100 mg. However, this comparison did not assess or adjust for potential clinical or methodological heterogeneity across trials. Therefore, we suggest that this finding be interpreted with caution.

Consistency. We found 1 fair-quality, placebo-controlled trial that examined the use of almotriptan 12.5 mg for treatment of 3 consecutive headaches.⁷¹ The results of this trial demonstrated that a significantly greater number of patients achieved 2-hour pain-free outcomes in 3 of 3 headaches with almotriptan 12.5 mg than placebo (18% compared with 5%; $P<0.05$).

Early intervention. The efficacy of almotriptan 12.5 mg administered early in a migraine, while pain is mild, has been demonstrated in 2 fair-quality placebo-controlled trials named Act when Mild ('AwM')⁷³ and Axert® Early Migraine Intervention Study ('AEGIS').⁷⁴ The 'AwM' trial was designed to compare early and non-early intervention and involved 4 treatment groups. For the purposes of this review, our interest was in the 2 treatment groups in which patients were randomized to administer treatment with almotriptan or placebo when pain was still mild and within 1 hour of onset. Results from the other 2 treatment groups, in which patients were randomized to administer treatment with almotriptan or placebo when pain was moderate to severe, were reported separately

and will not be discussed here. In the Axert® Early Migraine Intervention Study, patients were allowed to treat pain of any intensity, as long as it was within 1 hour of onset, but outcomes for mild and moderate-to-severe headaches were reported separately. In both trials, almotriptan was superior to placebo in rates of 2-hour pain-free and 24-hour sustained pain-free. Rate of 2-hour pain-free in ‘AwM’ was 49% for almotriptan and 25% for placebo (odds ratio 2.93; 95% CI, 1.62 to 5.31; $P=0.0004$), and in ‘AEGIS’ were 37% and 24%, respectively ($P=0.01$). Rate of 24-hour sustained pain-free was 46% for almotriptan and 16% for placebo in ‘AwM’, and in the ‘AEGIS’ trial was 25% and 16%, respectively ($P=0.040$). Based on our (EPC) independent random-effects meta-analysis, these findings correspond to a pooled relative risk of 1.71 (95% CI, 1.32 to 2.21) and a number-needed-to-treat of 6 for 2-hour pain-free outcomes. For 24-hour sustained pain-free rates, we calculated a pooled relative risk of 2.08 (95% CI, 1.12 to 3.86) and a number-needed-to-treat of 6. Functional disability and quality-of-life outcomes were also reported in a secondary publication of the ‘AEGIS’ trial.⁷² At 2 hours, mean functional disability scores showed that significantly more patients functioned normally with almotriptan than placebo (54% compared with 38%; $P=0.007$). At 24 hours, scores in all 5 domains of the Migraine Quality-of-life Questionnaire were consistently better for almotriptan than placebo.

Naratriptan

Direct comparisons

We included 2 head-to-head trials comparing naratriptan 2.5 mg with the conventional tablet form of sumatriptan 100 mg.^{29, 30} One was good quality³⁰ and the other was fair.²⁹ In the good quality trial, naratriptan 2.5 mg and the conventional tablet form of sumatriptan 100 mg had similar rates of 2-hour pain-relief (60% compared with 52%) and 2-hour no-or-mild disability (54% compared with 62%).³⁰ No statistical analyses were performed on 24-hour outcome data, but naratriptan 2.5 mg appeared to have a lower rate of recurrence (17% compared with 44%) and a similar rate of sustained relief (48% compared with 44%) compared with sumatriptan 100 mg. The fair-quality trial did not report pain outcomes at 2 hours,²⁹ but rates of 4-hour pain relief (76% compared with 84%) and 24-hour sustained relief (39% compared with 34%) were reported as similar for naratriptan 2.5 mg and the conventional tablet form of sumatriptan. Neither trial reported on pain-free, workplace productivity, or quality of life. Both trials looked at treatment of only 1 headache per patient and thus did not provide data on consistency of response across multiple headaches.

Placebo-controlled trials: Naratriptan

We found no placebo-controlled trials of naratriptan that reported quality of life, workplace productivity, or 2-hour or 24-hour pain-free outcomes. We also found no placebo-controlled trials that evaluated consistency of naratriptan across multiple headaches.

Reformulated (rapid-release) oral sumatriptan

Direct comparisons

We found no head-to-head trial directly comparing reformulated (rapid-release) oral sumatriptan tablet with any other triptan.

Placebo-controlled trials: Reformulated oral sumatriptan

We included placebo-controlled trials of reformulated oral sumatriptan that looked at early treatment of migraine while pain is still mild.^{78, 79} We also used data from placebo-controlled trials of reformulated sumatriptan 100 mg and the conventional tablet form of sumatriptan to explore indirect comparisons between the 2 formulations on 2-hour pain-free rates.

Early intervention.

The efficacy of reformulated sumatriptan 100 mg administered early in a migraine, while pain is mild, was demonstrated in a fair-quality trial of 432 adults who were instructed to administer treatment when pain was still mild and within 1 hour of onset.^{78, 79} Rate of 2-hour pain-free was 66% for reformulated sumatriptan 100 mg and 20% for placebo ($P<0.001$). At 24 hours, rate of sustained pain-free also was significantly greater for reformulated sumatriptan 100 mg than placebo (40% compared with 10%; $P<0.001$). From these data, we (EPC) calculated a relative risk of 3.38 (95% CI, 2.65 to 4.30) and a number needed to treat of 2 for 2-hour pain-free and a relative risk of 4.09 (95% CI, 2.83 to 5.92) and a number needed to treat of 3 for 24-hour sustained pain-free. Function and productivity outcomes from this trial were reported.⁷⁸ Compared with placebo, rate of normal function was significantly greater for reformulated sumatriptan 100 mg at 45 minutes (29% compared with 18%; $P<0.05$), 1 hour (50% compared with 25%; $P<0.001$), and 2 hours (60% compared with 28%; $P<0.001$). At 24 hours, significantly less time was lost on activities other than paid work for reformulated sumatriptan 100 mg (2.0 hours) than placebo (3.6 hours; $P<0.05$). However, lost time in paid work was similar for reformulated sumatriptan 100 mg and placebo (2.5 and 1.9 hours, respectively).

Indirect comparison of reformulated with the conventional tablet form of sumatriptan.

In the absence of head-to-head trials that directly compared reformulated and the conventional tablet form of sumatriptan, we explored indirect comparisons between formulations using data from placebo-controlled trials. Data from placebo-controlled trials of reformulated sumatriptan⁸⁰ and the conventional tablet form of sumatriptan^{36, 37, 45, 81-85} were pooled, and combined relative risks and numbers needed to treat were generated for each triptan for 2-hour pain-free rates. Estimates of relative risk were similar for the conventional tablet form of sumatriptan and reformulated sumatriptan and the large overlap of 95% confidence intervals did not suggest a clear advantage for either formulation over the other. However, the somewhat higher rate of 2-hour pain-free rates in the placebo group of the reformulated sumatriptan trial compared with those of the conventional tablet form of sumatriptan trials suggests the presence of at least some heterogeneity between the 2 sets of trials, likely in patient population or outcome assessment. Therefore, we caution against drawing firm conclusions about the comparison of reformulated and the conventional tablet form of sumatriptan until results from adjusted, quantitative, indirect comparisons, or head-to-head trials become available. We also sought results on 24-hour sustained pain-free outcomes from placebo-controlled trials of reformulated and the conventional tablet form of sumatriptan, but insufficient data were available from trials of conventional sumatriptan.

Sumatriptan injection and nasal spray

Direct comparisons

We included 2 head-to-head trials that compared injectable sumatriptan with the conventional oral formulation.^{42, 43} But because the trials were poor quality, their findings will not be discussed here. We found no head-to-head trials comparing sumatriptan nasal spray with any other triptan.

Placebo-controlled trials: Sumatriptan injection

Indirect comparisons of subcutaneous sumatriptan to oral formulations of other triptans. Sumatriptan is the only triptan approved in the United States and Canada in an injectable form. Given the lack of fair-quality or good-quality head-to-head trials involving subcutaneous sumatriptan 6 mg, we examined findings of a good-quality systematic review that qualitatively evaluated indirect comparisons between subcutaneous sumatriptan 6 mg and other triptans on the basis of unadjusted estimates of relative risk calculated for each triptan using pooled data from placebo-controlled trials.⁵² The main advantage of subcutaneous sumatriptan 6 mg over oral triptans is that it could potentially provide earlier pain relief. In 12 trials,^{86-89 90-96} pooled rates of 1-hour pain relief were significantly greater for subcutaneous sumatriptan 6 mg than placebo (70% compared with 22%), which resulted in the largest relative benefit estimate (3.2; 95% CI, 2.8 to 3.6) and a number needed to treat of 2.⁵² Benefits relative to placebo calculated for other triptans were lower, ranging from 1.6 (95% CI, 1.3 to 1.9) for oral the conventional tablet form of sumatriptan 100 mg to 2.3 (95% CI, 1.9 to 2.8) for eletriptan 40 mg.

Functional capacity, work productivity, and quality of life.

Numerous fair-quality, placebo-controlled studies of subcutaneous sumatriptan reported on functional capacity, work productivity, and quality of life.^{86-90, 92-106} Subcutaneous sumatriptan consistently reduced time to return to work,^{86, 89, 90, 94-96, 103} degree of clinical disability,^{87, 88, 93, 98, 99, 102, 105, 106} and time to emergency room discharge⁹⁸ and improved quality of life-related symptoms (contentment and vitality dimensions of the Minor Symptom Evaluation Profile).¹⁰²

Frovatriptan

Direct comparisons

We are aware of 1 head-to-head trial that directly compared frovatriptan 2.5 mg with the conventional tablet form of sumatriptan 100 mg.¹⁰⁷ However, information about this trial is available only in the form of an abstract, which did not provide adequate methodological detail for assessment of internal validity. Consequently, results from this trial were excluded from our review.

Placebo-controlled trials: Frovatriptan

Indirect comparisons of frovatriptan to other oral triptans.

Two-hour pain-free data from placebo-controlled trials were pooled and a combined risk difference for frovatriptan 2.5 mg and for the conventional tablet form of sumatriptan 100 mg were qualitatively compared. For the conventional tablet form of sumatriptan 100 mg, we conducted a risk difference meta-analysis of 8 placebo-controlled trials.^{36, 37, 45, 81-85} Compared with placebo (8%, 57/696), rates of 2-hour pain-free were 20% higher (95% CI, 0.16 to 0.25) for the conventional tablet form of sumatriptan 100 mg (30%, 437/1478), with a number needed to treat of 4. For frovatriptan 2.5 mg, we obtained the

risk difference estimate for 2-hour pain-free rates from a good-quality systematic review that pooled data from 5 placebo-controlled trials involving a total of 2866 patients.¹⁰⁸ Results of their risk difference meta-analysis indicate that rates of 2-hour pain-free were only 9% higher (95% CI, 0.07 to 0.10; number needed to treat of 12) for frovatriptan 2.5 mg (12%) compared with placebo (3%), indicating frovatriptan is probably inferior to the conventional tablet form of sumatriptan 100 mg.

Early intervention. One fair-quality, placebo-controlled, crossover trial of frovatriptan 2.5 mg reported results from 137 adults who took study medication in the early stage of their migraine.¹⁰⁹ Rate of 2-hour pain-free was better with frovatriptan 2.5 mg than placebo (28% compared with 20%; $P=0.04$), with a relative risk of 1.40 (95% CI, 1.11 to 1.76) and a number needed to treat of 12. Results of the comparison between frovatriptan 2.5 mg and placebo for rate of 24-hour sustained pain-free were not reported.

Key Question 1b. Fixed-dose combination tablets containing a triptan compared with triptan monotherapy

Direct comparisons

The only 2 head-to-head trials that involved Treximet® were both conducted as part of the new drug application program and were designed to meet the US Food and Drug Administration's minimum requirement for all fixed-dose combination products that the product show superiority to its individual components.¹¹⁰ Although sumatriptan tablets are commercially available in only 25 mg, 50 mg, and 100 mg strengths, in order to match the dosage strength for the sumatriptan component in Treximet®, these trials used an 85 mg dose for sumatriptan monotherapy. Both trials demonstrated that Treximet® 85 mg/500 mg was superior in efficacy to its individual components, sumatriptan 85 mg and naproxen 500 mg, on the primary outcome of sustained 24-hour pain-free response.¹¹⁰ Treximet® was also superior to sumatriptan 85 mg in improving patients' return to normal function, overall productivity, and satisfaction with overall effectiveness.¹¹¹ Whether Treximet® is superior to monotherapy with the commercially available 100 mg dosage of sumatriptan, or any other triptan, has not yet been directly evaluated in any known head-to-head trial.

Placebo-controlled trials: Treximet®

Placebo-controlled trials provided supplemental evidence on the efficacy of Treximet® in early treatment of migraine when pain is still mild.¹¹²⁻¹¹⁶

Early intervention. Treximet® is the most well-studied triptan for early treatment of mild migraine. The efficacy of Treximet® (rapid-release sumatriptan RT 85 mg/naproxen 500 mg) administered early in a migraine while the pain is still mild has been demonstrated in 6 trials (GlaxoSmithKline Protocols TRX101998, TRX101999, TRX103632, TRX103635, TRX106571, and TRX106573), enrolling a total of over 2700 adults. Methods and results for 2 pairs of protocols (TRX101998 and TRX101999; TRX103632 and TRX103635) are fully published in 2 journal articles, respectively.^{116, 117} Methods and results for protocols TRX106571 and TRX106573 had not yet been published at the time of this report, but were accessed from the summary reports available on the manufacturer's clinical trial registry website (<http://www.gskclinicalstudyregister.com>). Protocols TRX101998 and TRX101999 used parallel designs and were rated good

quality. Protocols TRX106571 and TRX106573 used crossover designs to specifically evaluate efficacy and harms in adults with a history of poor response or intolerance to previous triptan treatment. Protocols TRX106571 and TRX106573 were rated fair-quality mainly because the summary report only provided combined results for both crossover periods, which did not appear to be assessed or adjusted for potential order effects. Protocols TRX103632 and TRX103635 used 4-period crossover designs to evaluate consistency across 3 attacks.¹¹⁷

Patients were randomized to 1 of 5 treatment sequences, 4 of which contained 1 interspersed placebo treatment period. One sequence that contained 4 consecutive treatment periods of Treximet® was included for comparison in order to assess period effects and within-subject consistency. Results for protocols TRX103632 and TRX103635 were reported separately for the first period only and were rated good quality. Patients in all 6 trials were instructed to take trial medication within 1 hour of migraine onset and while the pain remained mild. In all 6 trials, Treximet® was superior to placebo on rates of 2-hour pain-free and 24-hour sustained pain-free. We (EPC) calculated separate pooled relative risk estimates for the subgroup of 4 trials (TRX101998, TRX101999, TRX103632, TRX103635; N=1537) that enrolled patients regardless of their triptan treatment history and for the subgroup of 2 trials, which required prior poor response or intolerance (TRX106571 and TRX106573; N=535). For 2-hour pain-free outcomes, compared to the combined estimate of benefit from the 4 trials that enrolled patients regardless of their prior triptan treatment history (relative risk, 3.12; 95% CI, 2.64 to 3.69), the benefit of Treximet® over placebo was somewhat smaller in the 2 trials which required prior poor response or intolerance to triptans (relative risk, 2.62; 95% CI; 1.92 to 3.58). For 24-hour sustained pain-free outcomes, however, compared with the combined estimate of benefit from the 4 trials of patients with an unspecified triptan treatment history (relative risk, 3.21; 95% CI, 2.63 to 3.91), the benefit of Treximet® over placebo was somewhat larger in patients with a prior history of poor response or intolerance to triptans (relative risk 3.77, 95% CI, 2.38 to 5.99).

Protocols TRX103632 and TRX103635 also evaluated within-subject consistency of 2-hour pain-free and 24-hour sustained pain-free outcomes in 973 of 1135 (86%) patients who treated at least 3 attacks with Treximet®.¹¹⁷ The rate of patients who were pain-free at 2 hours postdose in at least 2 of the first 3 attacks treated with Treximet® was 52% to 55% across both trials. The rates of patients with a sustained pain-free response through 24 hours postdose in at least 2 of the first 3 attacks treated with Treximet® ranged from 14% to 15% across the 2 trials. Subgroup analyses of the patients randomized to the sequence with no interspersed placebo treatment found similar rates of 2-hour pain-free and 24-hour sustained pain-free, which suggests against significant period effects. In patients randomized to the sequence that contained 4 consecutive treatment periods of Treximet®, 21% (18/84) in TRX103635 and 28% (27/95) in TRX103632 had 2-hour pain-free outcomes in all 4 attacks.

Open-label studies: Treximet®

The effect of Treximet® on quality of life was evaluated in one 12-month open-label study using the Migraine-Specific Quality of Life Questionnaire.¹¹⁸ Of the 600 patients enrolled, 565 (94%) treated at least 1 migraine and 362 (64%) completed the 12-month

trial and were included in the quality of life analyses. Measurement of clinically relevant improvement was based on changes of +6.80 points for the Role Restrictive domain score, +8.72 points for the Role Preventive domain score, and +5.76 points for the Emotional Function domain score. Proportions of patients who achieved clinically relevant improvements at 12 months were 60% for the Role Restrictive domain, 56% for the Role Preventive domain, and 64% for the Emotional Function domain.

Key Question 1c. Fixed-dose tablets containing a triptan compared with coadministration of its individual triptan and analgesic component agents

We found no evidence on the comparison of Treximet® and co-administration of its individual components, reformulated, rapid-release sumatriptan 85 mg and naproxen 500 mg.

Key Question 2. What are the comparative incidence and nature of complications (serious or life-threatening or those that may adversely effect compliance) of different triptans in adult patients being treated for migraine?

Key Question 2a. Monotherapy compared with monotherapy

There are no comparative studies concerning serious, life-threatening events associated with triptan use. But data on rare or life-threatening complications is available for the various forms of sumatriptan. A published review of the safety of sumatriptan examined adverse events in clinical trials and postmarketing surveillance data.¹¹⁹ In 1998, 16 serious cardiovascular events following use of subcutaneous sumatriptan and 11 following use of conventional oral sumatriptan were reported to the voluntary postmarketing surveillance system. In 1993, 103 serious cardiovascular events were reported for subcutaneous sumatriptan and 38 for conventional oral sumatriptan. The review concluded that “serious events including myocardial infarction, life-threatening disturbances of cardiac rhythm, and death have been reported within a few hours following the administration of sumatriptan. Considering the extent of use of sumatriptan in patients with migraine, the incidence of these events is extremely low.”

Data on rates of overall and specific adverse events from head-to-head trials—chest pain and central nervous system symptoms including dizziness, paresthesia, somnolence, and fatigue/asthenia—are summarized in Appendix E of the DERP report; there were no consistent differences between triptans. In most cases, descriptions of the methods used to assess intensity, duration, seriousness, and relationship to study medication were unclear or were not provided. Investigators generally described the adverse events as predominantly of mild to moderate severity and transient in nature.

Chest pain/tightness

Head-to-head trial results suggest a few differences among triptans in chest pain/tightness. In 1 trial,³⁶ chest pain was more frequent in patients taking sumatriptan 100 mg than rizatriptan 5 mg (6% compared with 1%; $P<0.05$) but did not differ from rizatriptan 10 mg (6% compared with 3%). Incidence of treatment-emergent chest pain was also significantly greater for the conventional oral form of sumatriptan 50 mg compared with almotriptan 12.5 mg (2.2% compared with 0.3%; $P=0.004$).⁶⁹ Subcutaneous sumatriptan 6 mg was associated with higher rates of mild to moderate chest pain than eletriptan 80 mg in 1 open trial of 1696 migraine headaches.¹²⁰

Central nervous system symptoms No significant between-group differences were reported by the trials that assessed dizziness, paresthesias, or somnolence. In 1 trial, fatigue/asthenia was more frequent in patients using sumatriptan 100 mg than those using rizatriptan 5 mg (8% compared with 2%; $P < 0.05$), but no difference was found between sumatriptan 100 mg and rizatriptan 10 mg (8% compared with 8%).³⁶

Key Question 2b. Fixed-dose combination tablets containing a triptan compared with triptan monotherapy

In Brandes 2007, adverse event rates that were reported in 2% or more patients in any treatment group were provided separately for the 2 trials comparing Treximet® with monotherapy consisting of reformulated sumatriptan, naproxen 500 mg, or placebo.¹¹⁰ There was no significant difference between Treximet® and monotherapy with reformulated sumatriptan 85 mg on rate of any adverse event, only dizziness, only paresthesia, or only somnolence. We pooled data from the trials and also found no significant difference in rate of any adverse event between Treximet® and monotherapy with reformulated sumatriptan 85 mg (27% [197/737] of patients using Treximet and 26% [194/735] of patients using reformulated sumatriptan 85 mg). We (EPC) also found no significant difference in rates of the adverse events dizziness, paresthesia, and somnolence, which were reported by 4% (28/737), 2% (18/737), and 3% (24/737), respectively, of patients using Treximet and 2% (16/735), 2% (17/735), and 2% (17/735), respectively, of patients using sumatriptan. In Study 1, rate of chest discomfort was 2% for Treximet® and 1% for reformulated sumatriptan 85 mg monotherapy. In Study 2, rate of chest discomfort was below 2% in both groups; thus, data was not reported.

Key Question 2c. Fixed-dose tablets containing a triptan compared with coadministration of its individual triptan and analgesic components

We found no evidence comparing Treximet® with co-administration of its components, reformulated, rapid-release sumatriptan RT 85 mg and naproxen 500 mg.

Key Question 3. Are there subgroups of patients based on demographics, other medications, or comorbidities for which one medication or preparation is more effective or associated with fewer adverse effects?

There is no evidence that any ethnic or racial group has a higher risk of adverse events from triptans or that one triptan has a particular advantage over others in any of these groups. Migraine is more common among women than men and in whites than blacks, and peaks in prevalence around age forty.¹²¹ We found no trials that included primarily men, blacks, or the elderly. However, the manufacturer of rizatriptan provided unpublished data on subgroups based on gender, age (< 40 years compared with ≥ 40 years), race (Caucasian or other), prophylactic treatment (any, beta-blockers, calcium channel blockers, tricyclic antidepressants, or valproate), and association with menstruation for 5 head-to-head trials comparing rizatriptan 10 mg with the conventional tablet form of sumatriptan,^{32, 33, 36} naratriptan 2.5 mg,³¹ and zolmitriptan 2.5 mg.³⁵ No statistical analyses were performed due to small sample sizes in these subgroups, so these findings should be considered exploratory and interpreted with caution.

Age

Unpublished data from head-to-head trials^{32, 33} provided by the manufacturer of rizatriptan suggested that 2-hour pain relief was higher for rizatriptan 10 mg than the conventional tablet form of sumatriptan 50 mg only in the subgroup of patients who were below 40 years in age, not in the subgroup age 40 and above. In other head-to-head trials rates of 2-hour pain relief were superior for rizatriptan regardless of age.^{31, 35, 36} Gender Unpublished data from head-to-head trials^{31-33, 35, 36} provided by the manufacturer of rizatriptan suggest that rate of 2-hour pain relief was higher for rizatriptan 10 mg than the conventional tablet form of sumatriptan 50 mg and 100 mg, naratriptan 2.5 mg, and zolmitriptan 2.5 in subgroups separating men and women.

Race

Unpublished data from head-to-head trials^{31-33, 35, 36} provided by the manufacturer of rizatriptan suggest that rates of 2-hour pain relief were higher for rizatriptan 10 mg than the conventional tablet form of sumatriptan 50 mg and 100 mg, naratriptan 2.5 mg, and zolmitriptan 2.5 in subgroups separating Caucasian and non-Caucasian adults.

In a 12-headache randomized placebo-controlled trial, subcutaneous sumatriptan was equally effective in whites, blacks, Hispanics, and others in relieving headache, reducing disability, and in adverse event rates.¹⁰⁰

Two placebo-controlled trials published in 2002^{122, 123} reported results of eletriptan and zolmitriptan in Japanese migraineurs. The trials enrolled samples similar in age, sex, and migraine history. Eletriptan and zolmitriptan had similarly better 2-hour pain relief, pain-free, and relief of associated symptoms (nausea, photophobia, phonophobia, vomiting); 24-hour recurrence; use of escape medication; and rate of adverse events (asthenia, paresthesia, somnolence) when each was compared with placebo. Outcome rates were within the ranges for eletriptan and zolmitriptan reported in head-to-head trials of predominantly white patients in otherwise similar samples.

Use of migraine prophylaxis

Results of pharmacokinetic trials, mostly in healthy volunteers, have been used to make recommendations for or against dosage adjustment in patients taking propranolol and other antimigraine drugs. Unpublished data from head-to-head trials comparing rizatriptan 10 mg with the conventional tablet form of sumatriptan 50 mg or 100 mg^{32, 36} provided by the manufacturer of rizatriptan suggest that in migraineurs rate of 2-hour pain-relief may be affected by whether or not patients use prophylactic migraine medication, especially tricyclic antidepressants or valproate. Rate of 2-hour pain-relief for rizatriptan 10 mg was greater than for the conventional tablet form of sumatriptan 100 mg in patients who were not using any prophylactic migraine treatments. However, in those who were using prophylactic migraine treatments, 2-hour pain relief was lower for rizatriptan 10 mg.

Other

Trials of triptans have generally excluded patients who have cardiovascular disease, uncontrolled hypertension, liver disease, and several other conditions. In general, triptans have proved to be as effective for migraine associated with menstruation as for other attacks. A double-blind, placebo-controlled randomized controlled trial demonstrated the effectiveness of subcutaneous sumatriptan in menstrual migraine.⁹¹

Retrospective meta-analysis of randomized controlled trials of rizatriptan, zolmitriptan, and subcutaneous sumatriptan support the view that triptans are equally effective for headache during menstruation as in other migraine headaches.¹²⁴⁻¹²⁶

We identified 1 double-blind randomized controlled trial of a triptan to prevent migraines associated with menses.¹²⁷ In this trial, across 4 menstrual periods, more patients treated with naratriptan 1 mg were headache-free than with placebo (23% compared with 8%). An earlier pilot study by the same investigator used sumatriptan for prophylaxis of menstrual migraine, but that study was uncontrolled.¹²⁸

In small subgroups of adults with menstruation-associated migraines from 2 head-to-head trials, both rizatriptan 10 mg and the conventional tablet form of sumatriptan 50 mg were superior to placebo in improving rate of 2-hour pain relief. But, in the menstruation-associated migraine subpopulations, rizatriptan 10 mg was no longer statistically superior to sumatriptan 50 mg as it was in the study population overall.^{32, 33}