CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-317

MEDICAL REVIEW

MEDICAL OFFICER GLOBAL SAFETY REVIEW UPDATE
Division of Over-The-Counter Drug Products

NDA: 21-317

NAME: Extra Strength Bayer® Migraine (500 mg Buffered Aspirin)

SPONSOR: Bayer Consumer Care; Morristown, NJ 07962

TYPE OF SUBMISSION: Commercial Pharmaceutical

DATE OF SUBMISSION: December 15, 2000

DATE OF REVIEW: September 28, 2001

REVIEWER: Rosemarie Neuner, MD,MPH

Executive Summary:

Bayer Consumer Care, the manufacturer of Extra Strength Bayer® Plus Aspirin (500 mg buffered aspirin), has filed this NDA in the hopes of obtaining a new migraine indication for this product. The product is currently labeled for the temporary relief of the pain of headache, sinusitis, colds, muscular aches, menstrual discomfort, toothaches and minor arthritis pain. It has been marketed in the United States by the Bayer Corporation for the past 10 years under 53 FR 46204 the Tentative Final Monograph for Internal Analgesic, Antipyretic, and Antirheumatic Drug Products (publication date November 16, 1988). The sponsor would like to market a stand alone product for the treatment of migraine headache and associated symptoms such as nausea, phonophobia, and photophobia called Extra Strength Bayer® Migraine. [redacted]

Safety information, from 4 articles identified via a worldwide literature search from the mid-1960's to August 2000, as well as 16 postmarketing adverse event case reports in migrainuers from April 1, 1985 to July 27, 2001, are reviewed and discussed in this safety update. Based on the information submitted by the sponsor no new or unexpected adverse events associated with the use of aspirin in the treatment of migraine were, thus, identified.

Final Recommendation:

Review of the global safety data submitted by the sponsor in support of aspirin's safety profile in the treatment of migraine does not reveal any additional information regarding this product's safety profile in migraine patients. Based on the information reviewed the current safety warnings for aspirin are appropriate and do not need to be changed or updated. The absence of safety data in support of menstrual migraine warrants against approval of the sponsor's proposed line extension for this product. Additional safety and efficacy information in support of a menstrual migraine claim would be required from the sponsor if they want to pursue this indication.

APPEARS THIS WAY
ON ORIGINAL

Background

This medical officer review is a global safety profile update of Extra Strength Bayer® Plus Aspirin (500 mg buffered aspirin) that was done as part of the Agency's overall review of Bayer Consumer Care's submission, NDA 21-317, in which they have requested a migraine indication for this product. Extra Strength Bayer ® Plus Aspirin is an over-the-counter (OTC) analgesic product formulated as an immediate-release bilayer caplet comprised of 500 mg of acetylsalicylic acid (aspirin) with calcium carbonate as a buffering agent. It has been marketed in the United States by the Bayer Corporation for the past 10 years under 53 FR 46204 the Tentative Final Monograph for Internal Analgesic, Antipyretic, and Antirheumatic Drug Products (publication date November 16, 1988). This product is currently labeled for the temporary relief of the pain of headache, sinusitis, colds, muscular aches, menstrual discomfort, toothaches and minor arthritis pain. The recommended dose for this formulation is 1 or 2 caplets with water every 4 to 6 hours as needed up to 8 caplets in 24 hours, or as directed by a doctor, in adults and children age 12 and over. It is not indicated for use in children under 12 unless directed by a doctor.

Pending a regulatory decision, the sponsor is proposing to market a stand alone aspirin product for the treatment of migraine headache and associated symptoms such as nausea, phonophobia, and photophobia called Extra Strength Bayer® Migraine [redacted] Both of these proposed products would have the following dosing directions for adults 18 years and over: 2 caplets with a full glass of water not to exceed 8 caplets in 24 hours unless directed by a doctor. Individuals under 18 years of age, are to consult a doctor.

In June 2000 an effervescent formulation of Extra Strength Bayer® Aspirin was approved for the treatment of migraine in Germany. According to the sponsor approximately [redacted] tablets of this product were sold in Germany over the 13 month time period covered from June 1, 2000 through July 31, 20001.

In support of this application, the sponsor has submitted for Agency review the following safety information:

1. The safety database from the 3 randomized, placebo-controlled, single dose migraine efficacy studies and 1 biopharmaceutical study contained in this submission (Study Numbers S98-072, S98-073, S98-074, and S99-102).

2. The results of a worldwide literature search of published randomized clinical trials which studied single-ingredient aspirin in the treatment or prophylaxis of migraine headache for the period from the mid-1960's to August 2000.

3. Postmarketing adverse event data collected by the Bayer Corporation's European drug safety division associated with any/all aspirin containing compounds that occurred when used to treatment a migraine during the time period from April 1, 1985 to July 27, 2001.

Since a review of the clinical trial safety database contained in this submission can be found in the medical officer's efficacy review dated 6/12/01 by Dr. Kevin A. Prohaska of HFD-120, this safety profile update will focus on the remaining 2 sources of safety data as listed above.

I. Published randomized clinical trials which studied single-ingredient aspirin in the treatment or prophylaxis of migraine headache for the period from the mid-1960's through August 2000.

In support of Extra Strength Bayer® Plus Aspirin safety profile the sponsor submitted the following published 27 references that were identified via a worldwide literature search during the period from the mid-1960's through August 2000:

1. Vein A, Voznesenskaya T, Danilov A. The effects of aspirin on the CNV in healthy individuals. Cephalalgia 1995; 15(2):129-31.
2. Ross-Lee L, Eadie MJ, Tyrer JH. Aspirin treatment of migraine attacks: clinical observations. Cephalalagia 1982; 2(2):71-6.
3. Bone I, Durward WF, Hind VM. Possible danger of aspirin therapy in presence of migraine. Lancet 1978; 2(8091):680.
4. Limmroth V, Katsarava Z, Diener HC. Acetylsalicylic acid in the treatment of headache. Cephalalgia 1999; 19(6):545-551.
5. Hakkarainen H, Quiding H, Stockman O. Mild analgesics as an alternative to ergotamine in migraine. A comparative trial with acetylsalicylic acid, ergotamine tartrate, and a dextropropoxyphene compound. J Clin Pharmacol 1980; 20(10):590-595.
6. Antonaci F, Sances G, Manni R, Buzzi MG. Epileptic seizure during aspirin and caffeine withdrawal in a drug induced headache. Funct Neurol 1996; 11(6):333-337.
7. Miceli G, Manzone GC, Granella F, et al. Clinical and epidemiological observations on drug abuse in headache patients. Diener HC, Wilkinson Mes. Drug-induced headache. Berlin, Heidelberg; Springer Verlag 1988:20-28.
8. Baumgartner C, Wessely P, Bingol C,et al. Long-term prognosis of analgesic withdrawal in patients with drug-induced headaches. Cephalalgia 1989: 29:510-519.
9. Lipton RB, Stewart WF, Ryan RE Jr, Saper J, Silberstein S, Sheftell F. Efficacy and safety of acetaminophen, aspirin, and caffeine in alleviating migraine headache pain: three double-blind, randomized, placebo-controlled trials. Arch Neurol 1998: 55(2):210-217.
10. Silberstein SD, Armellino JJ, Hoffman HD, Battickha JP, Hamelsky SW, Stewart WF, Lipton RB. Treatment of menstruation-associated migraine with the onprescription combination of acetaminophen, aspirin, and caffeine: results from three randomized, placebo-controlled trials. Clin Ther 1999; 21(3):475-491.
11. Goldstein J, Hoffman HD, Armellino JJ, Battikha JP, Hamelsky SW, Couch J, Blumenthal H, Lipton RB. Treatment of severe, disabling migraine attacks in an over-the-counter population of migraine sufferers: results from three randomized, placebo-controlled studies of the combination of acetaminophen, aspirin, and caffeine. Cephalalgia 1999;19(7):684-691.
12. Schoenen J, Lenaerts M, Bastings E. High-dose riboflavin as a prophylactic treatment of migraine: results of an open pilot study. Cephalalgia 1994;14(5):328-329.
13. Tfelt-Hansen P, Henry P, Mulder LJ, Scheldewaet RG, Schoenen J, Chazot G. The effectiveness of combined oral lysine acetylsalicylate and metoclopramide compared with oral sumatriptan for migraine. Lancet 1995;346(8980):923-926.
14. Chabriat H, Joire JE, Danchot J, Grippon P, Bousser MG. Combined oral lysine acetylsalicylate and metoclopramide in the acute treatment of migraine: a multicenter double-blind placebo controlled study. Cephalalgia 1994;14(4):297-300.
15. Hugues FC, Lacoste JP, Danchot J, Joire JE. Repeated doses of combined oral lysine acetylsalicylate and metoclopramide in the acute treatment of migraine. Headache 1997;37(7):452-454.
16. Le Jeunne C, Gomez Jp, Pradalier A, Titus I Albareda F, Joffroy A, Liano H, Henry P, Lainez Jm, Geraud G. Comparative efficacy and safety of calcium carbasalate plus metoclopramide versus ergotamine tartrate plus caffeine in the treatment of acute migraine attacks. Eur Neurol 1999;41(1):37-43.
17. Catheline JM, Guiberteau/Canfrere V, Zarka O, Le Borgne J, Lehur PA. [Rectal stenosis following prolonged use of suppositories of acetylsalicylic acid and paracetamol. Correction by perineal approach]. Ann Chir 1995;49(6):551. [Article in French.]
18. Van Gossum A, Zalcman M, Adler M, Peny MO, Houben JJ, Cremer M. Anorectal stenosis in patients with prolonged use of suppositories containing paracetamol acetylsalicylic acid. Dig Dis Sci 1993;38(11):1970-1977.
19. Diener HC. Efficacy and safety of intravenous acetylsalicylic acid lysinate compared to subcutaneous sumatriptan and parenteral placebo in the acute treatment of migraine. A double-blind, double-dummy, randomized, multicenter, parallel group study. The ASASUMAMIG Study Group. Cephalalgia 1999:19(6)581-588.
20. Limmroth V, May A, Diener H. Lysine-acetysalicylic acid in acute migraine attacks. Eur Neurol 1999;41(2):88-93.

21. McGinnis J, Seaton TL. What is the optimal strategy for managing acute migraine headaches? J Fam Pract 2001 Feb;50(2):176.
22. Tfelt-Hansen P. The effectiveness of combined oral lysine acetylsalicylate and metoclopromide (Migpriv) in the treatment of migraine attacks. Comparison with placebo and oral sumatriptan. Funct Neurol 2000;15 Suppl 3:196-201.
23. Gedye A. Hypothesis treatment for migraines using low doses of tryptophan, niacin, calcium, caffeine, and acetylsalicylic acid. Med Hypotheses 2001 Jan;56(1):91-4.
24. Krumholz W, Szalay G, Ogal H, Menges T. [Effect of migraine medications on monocyte chemotaxis]. [Article in German.] Anaesthesiol Reanim 2000;25(4):102-4.
25. Lange R, Schwarz JA, Hohn M. Acetylsalicylic acid effervescent 1000 mg (aspirin) in acute migraine attacks; a multicenter, randomized, double-blind, single-dose, placebo-controlled parallel group study. Cephalalgia 2000 Sep;20(7):663-7.
26. High Doses of Acetylsalicylic Acid for Migraines A Classic New Format Symposium on "Autonomous Migraine Management" Kiel. MMW Advances in Medicine June 2000.
27. Lipton RB, Stewart WF, Stone AM, Lainez MJ, Sawyer JP. Stratified care vs step care strategies for migraine: the Disability in Strategies of Care (DISC) Study: A randomized trial. JAMA 2000 Nov 22-29;284(20):2599-605.

Review of the 27 references listed above revealed that 23 of them were unable to provide evidence in support of Extra Strength Bayer® Plus Aspirin's safety profile. Seventeen of these 23 references were identified as being inappropriate because they studied formulations or combinations of acetylsalicylic acid that were different from the sponsor's current formulation. Of these 17 references, 9 references describe migraine studies involving formulations of acetylsalcylic acid that contained lysine (Articles 13, 14, 15, and 22), were given concomitantly with metoclopromide (Articles 16, 19, 20, and 27), or at low-doses with riboflavin (Article 12). Another 6 references from this group describe clinical trials which studied aspirin-caffeine combinations in migraineurs (Articles 6, 8, 9, 10,11, and 23). The remaining 2 references (Articles 17 and 18) from this group describe cases of rectal stenosis that were directly related to the route of drug administration (i.e., rectal suppositories) which is different from that of the product under review. The other 5 references were found to be unsuitable for the following reasons: Article 1 described a neurological study involving the use of acetylsalicylic acid in normal subjects and not migraineurs, Articles 4 and 7 do not contain any safety information that could be used in support of aspirin's safety profile, and Articles 21 and 26 contain duplicated information since they summarize clinical trials that were also listed as references. Since the sponsor failed to provide an english translation of Article 24 (in German), it could not be reviewed. Thus, the following discussion will be limited to the 4 remaining references (Articles 2, 3, 5, and 25). Synopses of these references can be found in Appendix I at the end of this review.

The article by Ross-Lee et al[2] described the results generated from a retrospective, uncontrolled, observational survey study of 61 migraine patients who used aspirin to treat their migraine attacks. Forty-four (44) out of the 45 patients who completed the study's questionnaire which covered a variety of aspects related to aspirin therapy, supplied information regarding aspirin-related adverse events. A total of 7 subjects reported experiencing an adverse event associated with the use of aspirin therapy which included nausea (16%; 7/44) and an unpleasant taste (2%; 1/44). The article did not specify the formulation of aspirin used by the 7 migraineurs who reported these adverse events. In their letter to the editor, Bone et al[3] discuss the case of a 58-year old male with a 20 year history of migraines who developed a cerebral infarction following the use of low-dose aspirin for antiplatelet therapy. Although the authors are unable to directly attribute the patient's cerebral infarct to his low-dose aspirin therapy, they raise the possibility of a drug safety issue associated with aspirin's anticyclo-oxygenase activity and the cerebral vasculature. They postulate that since aspirin can cause vasoconstriction due to its ability to inhibit cyclo-oxygenase activity, it could possibly induce localized cerebral vasoconstriction when used at high doses in the treatment of migraine resulting in a cerebral infarction such as their patient experienced.

The randomized, double-blind, crossover study by Hakkarainen et al[5] evaluated the effectiveness of 1 mg ergotamine tartrate versus 500 mg acetylsalicyclic acid and a

dextropropoxyphene compound comprised of 100 mg dextropropoxyphene, 350 mg acetylsalicyclic acid, and 150 mg phenoxyphene in the treatment of 25 female migraineurs. The incidences of the most commonly reported side effects experienced by the study participants during the trial are listed in the following table created by the authors', Table 1.

Table 1 – Study Authors' Tabular Listing of Adverse Event Incidences Associated With All Treatments[5]

Drug	Nausea (%)	Nausea and vomiting (%)	Gastric discomfort (%)	Dizziness (%)	Fatigue (%)	Other (%)
Ergotamine tartrate	38.9	14.8	11.4	5.7	10.3	0.6
Dextropropoxyphene compound	23.4	5.7 #	5.7	9.7	14.3	--
Acetylsalicylic acid	35.4	16.0#	10.9	7.4	13.7	--

[5] Hakkarainen H, Quiding H, Stockman O. Mild analgesics as an alternative to ergotamine in migraine. A comparative trial with acetylsalicylic acid, ergotamine tartrate, and a dextropropoxyphene compound. J Clin Pharmacol 1980; 20(10):590-595.

Statistically significant difference at $p<0.001$ via Friedman's analysis of variance

Statistically significant difference at $p<0.01$ via Friedman's analysis of variance

Review of the adverse event data shown above demonstrates that the incidence of nausea and vomiting associated with the dextropropoxyphene compound was significantly lower as compared to ergotamine tartrate ($p<0.001$) and acetylsalicyclic acid ($p<0.01$). Further analysis of the study's safety data failed to reveal any significant differences in the incidences of the other reported drug-induced side effects.

The study by Lange et al[25] was a randomized, double-blind, placebo-controlled study which compared the effectiveness of a single 1000 mg dose of an effervescent acetylsalicylic acid formulation versus effervescent placebo in the treatment of migraine headache. Three hundred forty-three (343) patients completed the study out of the 374 patients that were randomized into the 2 treatment groups. A total of 14 out of 169 (8.3%) patients treated with effervescent acetylsalicyclic acid versus 5 out of 174 (2.9%) patients treated with placebo reported experiencing adverse events during the trial. The following table, Table 2, is a tabular listing of the adverse events reported by subjects to have occurred during this study. (Note: This adverse event data was not included in the text of the published article, but it was made available by the sponsor with the other safety information contained in the submission since they funded this trial.)

Table 2 – Tabular Listing of Adverse Events Reported by Subjects Treated With Effervescent Acetylsalicyclic Acid Versus Placebo in the Migraine Study by Lange et al[25]*

Adverse Event	Effervescent Acetylsalicyclic Acid Group (n=169)	Placebo Group (n=174)
Abdominal pain	1	1
Asthenia	0	1
Bronchitis	1	0
Diarrhea	1	0
Dizziness	1	1
Flu syndrome	1	0
Gastroenteritis	1	0
Glaucoma	0	1
Hypertension	1	0
Hypertonia	1	0
Hypertrophy of skin	1	0
Hyperthyroidism	0	1
Injury (accidental)	1	0
Laryngitis	2	0
Nausea	0	1
Nausea and vomiting	1	0
Neck pain	1	1
Otitis externa	0	1
Pain	1	0
Pharyngitis	1	0
Tendon disorder	2	0
Total Number	18	9

[25]Lange R, Schwarz JA, Hohn M. Acetylsalicylic acid effervescent 1000 mg (aspirin) in acute migraine attacks; a multicenter, randomized, double-blind, single-dose, placebo-controlled parallel group study. Cephalalgia 2000 Sep;20(7):663-7.

*Some patients reported experiencing more than 1 adverse event during the study.

Although relatively few adverse events were associated with either of the treatment groups in this single-dose study, the overall incidence of adverse events reported by the effervescent acetylsalicyclic group (8%) was higher than the placebo group (3%). On statistical analysis, the difference between the 2 treatment groups was found to be significant ($p<0.03$ calculated via Chi square) but not clinically relevant since the individual numbers and the types of events were low and similar for both groups.

Medical Reviewer's Comments: *Review of the published literature submitted by the sponsor failed to identify any new or unexpected adverse events associated with the use of aspirin in the treatment of migraine headache. Although the case report published by Bone et al[3] raises the possibility of an increase in the risk of thrombotic cerebrovascular events in migraine patients who use high doses of aspirin to treat their migraine, this phenomena has not been confirmed despite the 20 years that have passed since its publication. Its not clear to this reviewer if the patient they reported had a hemorrhagic stroke due to aspirin's antiplatelet effects instead of a bland infarct since the article does not mention if the patient underwent a CT scan of the brain to confirm the authors diagnosis.*

II. **Postmarketing adverse event data collected by the Bayer Corporation's European drug safety division associated with any/all aspirin containing compounds that occurred when used to treatment a migraine during the time period from April 1, 1985 to July 27, 2001.**

The sponsor submitted 16 case reports of adverse events which occurred in consumers who used aspirin to treat migraine that they had collected in their international safety database during the time period from April 1, 1985 to July 27, 2001. The following table, Table 3, is a tabular listing of these 16 cases. Two of the 16 cases involved the use of aspirin and caffeine containing analgesic compounds while the remaining 14 cases were associated with varying dosages of single-ingredient aspirin products.

Table 3 - Reviewer's Table of Adverse Events Associated with the Use of Aspirin Containing Products in the Treatment of Migraine.

Report Number	Age/Sex	Adverse Event
Acetylsalicylic acid with codeine phosphate and caffeine (Dolviran)		
1198610521	Unknown female	Developed chest pain and anxiety while taking unknown amount of aspirin containing compound. The patient recovered.
Acetylsalicylic acid (≤ 100 mg)		
200090049BVD	61 year old male	Developed gastrointestinal bleeding and hemorrhage status post 2 doses of 1000 mg of ASA orally. The patient recovered.
Acetylsalicylic acid (≥ 100 mg)		
1198910064	68 year old female	Developed dyspnea, cyanosis and apnea following the ingestion of 500 mg orally of ASA. No further information supplied regarding possible history of ASA allergy. The patient recovered.
1199711331	36 year old female	Developed erythema nodosum following the oral ingestion of 500 mg of ASA. No past medical history given. The patient recovered.
119971167	26 year old male	Developed gastric symptoms and nonspecified gastrointestinal disorder status post oral ingestion of an undetermined amount of ASA. Line listing noted history of drug abuse. The patient improved with treatment.
1199842921	56 year old female	Developed a duodenal ulcer and melena following the ingestion of an unknown amount of ASA orally. The patient recovered.
1199844775	32 year old male	Developed erythema exudativum multiforme major (Stevens Johnson Syndrome) following the ingestion of an unknown amount of ASA orally. The patient recovered.
200004601GDS	21 year old male	Developed a nose bleed (epistaxis) following the ingestion of an unknown amount of ASA capsule orally. The patient recovered.
200008458GDS	18 year old female	Developed ringing in the ears (tinnitus) following the ingestion of an unknown amount of ASA orally. The patient recovered.
200011575GDS	33 year old female	Developed itching on the bottom of the feet (pruritus) and anxiety following the ingestion of a single dose of 975 mg of ASA orally. The patient recovered.
200011576GDS	33 year old female	Developed hives and urticaria following the ingestion of a single dose of 975 mg ASA orally. The patient recovered.
200050155BVD	66 year old female	Developed abdominal pain, dyspepsia, coffee ground vomiting (hematemesis), tarry stools (melena), and gastrointestinal bleeding due to peptic ulcer hemorrhage following the ingestion of an unknown amount of ASA orally. No past medical history given. The patient recovered.
200051760BVD	25 year old female	Developed an acute allergic reaction of the face with itching (pruritus), edema, angioedema, and watery eyes following the ingestion of an unknown amount of an effervescent formulation of ASA orally. No past medical history given. The patient recovered.
200052220BVD	30 year old female	Developed palpitations, tinnitus, tiredness and an unspecified circulatory disorder following the ingestion of 1000 mg of ASA orally. The patient recovered.
200113836GDS	61 year old female	Developed bleeding duodenal ulcer with abdominal pain and melena following the ingestion of 500 mg per day of aspirin for migraine. Other medications include diclofenac 50 mg, almagate and amlodipine besilate. The patient recovered.
Acetylsalicylic acid with caffeine		
1199410014	51 year old male	Developed ulcerative colitis involving the recto-sigmoid colon following the ingestion of an unknown amount of an ASA-caffeine product orally. No past medical history given. The patient improved.

Seven out of these 16 cases were classified as serious in nature. Four (Report Numbers: 200090049BVD, 1199842921, 200050155BVD, and 200113836GDS) out of these 7 serious cases developed gastrointestinal bleeding which is a well known adverse event associated with aspirin. The case of the 61 year-old female (Report Number 200113836GDS) who developed a bleeding duodenal ulcer while taking 500 mg a day of aspirin was confounded by the concomitant use of diclofenac, another member of the nonsteriodal anti-inflammatory class of drugs, which can also cause gastrointestinal bleeding. Of the 3 remaining serious cases, 2 consumers (Report Numbers: 1198910064 and 200051760BVD) developed severe allergic and anaphylactic reactions after ingesting aspirin. Both of these patients recovered. Aspirin allergies have been reported and consumer warnings about this phenomena are required as part of the labeling of aspirin containing products. The last serious case (Report Number: 1199844775) developed Steven Johnson Syndrome after taking an unknown amount of aspirin. The patient recovered and no additional information was contained in the submitted case report forms.

Table 3 shown above, lists 9 case reports that were classified as nonserious in nature. Three (Report Numbers: 200011575GDS, 200011576GDS, and 1199711331) out of these 9 nonserious cases developed minor allergic and skin reactions after ingesting aspirin. Two other patients (Report Numbers: 200008458GDS and 200052220BVD) developed tinnitus which is a dose related side effect of aspirin. One report (Report Number: 200004601GDS) described a case of epistaxis (nosebleed) due to aspirin's anti-platelet effects that was nonserious in nature. There were also 2 nonserious reports (Report Numbers: 119971167 and 1199410014) involving cases of mild gastrointestinal upset and the development of ulcerative colitis. It is impossible to make any inferences of causality based on the limited information contained in the submitted report for the latter case. The last nonserious case (Report Number: 1198610521) involved a female patient age unknown who developed chest pain (tightness) and anxiety after taking an unknown amount of an aspirin-codeine-caffeine compound. Caffeine is a central nervous stimulant and could be responsible for the patient's symptoms.

Medical Reviewer's Comments: *Review of these 16 post marketing case reports does not reveal any additional information regarding aspirin's safety profile when used in the treatment of migraine. The small number of case reports related to already labeled adverse events (i.e., gastrointestinal bleeding, allergic reactions, and tinnitus) suggests that the current warnings for aspirin are appropriate and do not need to be changed or updated.*

Final Recommendations: Review of the global safety data submitted by the sponsor in support of aspirin's safety profile in the treatment of migraine does not reveal any new or unexpected adverse events for this product. [redacted] Based on the information reviewed, the current safety warnings for aspirin are appropriate and do not need to be changed or updated. [redacted]

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APPENDIX I

Ross-Lee L, Eadie MJ, Tyrer JH. Aspirin treatment of migraine attacks: clinical observations. Cephalalagia 1982; 2(2):71-6.

This was an uncontrolled, retrospective, observational study that assessed the efficacy of aspirin in the treatment of migraine. Study investigators reviewed the medical records from a neurological consulting practice and identified 87 migrainuers who had been instructed to take 3-4 tablets of aspirin at the onset of a migraine attack. A total of 61 out of the 87 patients (70%) thus identified either had adequate information regarding their response to aspirin therapy recorded in their charts (15 patients) or completed a study questionnaire (45 patients) that was sent to them by the investigators for study inclusion. (Note: A summary of the study questionnaire was not included in the article.) A total of 42 out of the 61 patients (69%) enrolled in the study reported that aspirin provided some form of relief from their migraine attacks as follows: 27 patients (44%) usually or always effective; 15 patients (25%) sometimes effective; and 19 patients (31%) rarely or never effective. Analysis of the study data revealed that patients' response to aspirin therapy was found to be statistically correlated with 2 parameters: the amount of aspirin ingested ($p<0.05$), and the occurrence of an aura ($p<0.005$). No statistical correlation was noted on analysis of the following parameters: sex ($p>0.40$), age at onset of migraine or at time of referral ($p>0.05$), duration of migraine history ($p>0.05$), severity of migraine ($p>0.05$), family history of recurrent headaches ($p>0.5$), or the occurrence of associated nausea ($p>0.30$) or vomiting ($p>0.40$) during migraine attacks. Only 7 patients (16%) reported experiencing drug-related side effects associated with aspirin that included an unpleasant taste (1 patient) and nausea (7 patients). The authors suggest that the latter may have been due to the patients' migraines and not the aspirin therapy. They conclude that migrainuers with auras are able to medicate themselves early on during the course of their attacks thus increasing their chances of a positive response to aspirin therapy.

Bone I, Durward WF, Hind VM. Possible danger of aspirin therapy in presence of migraine. Lancet 1978; 2(8091):680.

In this letter to the editor, the authors discuss the case of a 58 year-old patient with a 20-year history of classical migraine headaches, one episode of reversible ischemic neurologic deficit (RIND) manifested by a right hemisensory disturbance, and peripheral arterial occlusion following a negative angiographic work-up for the RIND, who went on to develop a cerebral infarction despite prophylactic antiplatelet therapy with aspirin. The patient presented with a persistent right lower homonymous quandrantic field deficit consistent clinically with a cerebral infarction. The neurological deficit developed during a typical migraine attack after 2 years of aspirin therapy for the above events (325 mg twice a day). Although the authors do not rule-out the possibility of degenerative vascular disease as the etiology of the patient's cerebral infarction, they suggest that high dose aspirin may have been responsible. Their theory is based on aspirin's ability to inhibit the cyclo-oxygnease pathway resulting in decreased amounts of vessel-wall prostacyclin that could possibly increase the risk of cerebral vasocculsion in migrainuers since both the prodroma and the migraine attack are thought to be due to abnormal platelet aggregation. They, therefore, suggest that the dose of aspirin used in migraine studies be adjusted accordingly.

Hakkarainen H, Quiding H, Stockman O. Mild analgesics as an alternative to ergotamine in migraine. A comparative trial with acetylsalicylic acid, ergotamine tartrate, and a dextropropoxyphene compound. J Clin Pharmacol 1980; 20(10):590-595.

This was a randomized, double-blind, double-dummy, crossover study which evaluated the effectiveness of acetylsalicylic acid (500 mg), ergotamine tartrate (1 mg), and Doleron novum, a dextropropoxyphene compound (100 mg dextropropoxyphene napsylate, 350 mg acetysalicylic acid, and 150 mg phenazone), in the treatment of acute migraine. Twenty-five (25) adult female

patients with histories of at least 2 migraine attacks per month were enrolled in the study. The study protocol required that each patient receive a total of 7 outpatient treatments with each one of the above study medications for 21 consecutive migraine attacks, thus generating data from 525 migraine attacks. Study data was collected via patient diaries that each subject was required to fill out during the course of the trial on the following 8 study parameters: number of doses taken, prevention of attacks, intensity of attacks, duration of attacks, working ability, patients' drug preference, and drug-induced side effects.

Analysis of the study data revealed that 86% of the patients took both doses of the acetylsalicylic acid as compared to 56% of the dextropropoxyphene compound and 63% of the ergotamine tartrate. These differences were found to be statistically significant when treatments with the dextropropoxyphene compound ($p<0.001$) and ergotamine tartrate ($p<0.01$) were compared to acetylsalicylic acid but not when they were compared to each other. Comparative analysis demonstrated that treatment with either dextropropoxyphene compound or ergotamine tartrate was equally effective in preventing migraine attacks, however both treatments were significantly more effective than acetylsalicylic acid in preventing attacks ($p<0.01$; and $p<0.001$ respectively). Although treatment with ergotamine tartrate was shown to be as effective as either acetylsalicylic acid or dextropropoxyphene compound in decreasing both the intensity and the duration of migraine attacks, treatment with the dextropropoxyphene compound was significantly better than acetylsalicylic acid for both of these parameters ($p<0.05$; and $p<0.01$ respectively). Regarding working ability, the study did not reveal any significant differences on comparison of treatment with ergotamine tartrate versus dextropropoxyphene compound or acetylsalicylic acid but further analysis demonstrated that treatment with dextropropoxyphene compound was significanctly better than with acetylsalicylic acid ($p<0.05$) for this parameter. Overall there was a significant difference in the patients' preferences for treatment with either dextropropoxyphene or ergotamine tartrate as compared to acetylsalicylic acid ($p<0.001$; and $p<0.01$ respectively). Study authors' Table 2 shown below is a tabular listing of the side effects and their incidences during the study. The lowest incidence of nausea and vomiting was associated with the dextropropoxyphene compound. This incidence was shown to be significantly different as compared to both ergotamine tartrate ($p<0.001$) and acetylsalicylic acid ($p<0.01$). Further analysis of the study's safety data failed to reveal any significant differences in the incidences of the other reported drug-induced side effects.

Table 1 – Study Authors' Tabular Listing of Adverse Event Incidences Associated With All Treatments[5]

Drug	Nausea (%)	Nausea and vomiting (%)	Gastric discomfort (%)	Dizziness (%)	Fatigue (%)	Other (%)
Ergotamine tartrate	38.9	14.8	11.4	5.7	10.3	0.6
Dextropropoxyphene compound	23.4	5.7	5.7	9.7	14.3	--
Acetylsalicylic acid	35.4	16.0	10.9	7.4	13.7	--

[5] Hakkarainen H, Quiding H, Stockman O. Mild analgesics as an alternative to ergotamine in migraine. A comparative trial with acetylsalicylic acid, ergotamine tartrate, and a dextropropoxyphene compound. J Clin Pharmacol 1980; 20(10):590-595.

* Statistically significant difference at $p<0.001$ via Friedman's analysis of variance

Statistically significant difference at $p<0.01$ via Friedman's analysis of variance

Based on the data generated from this study the authors conclude that the dextropropoxyphene compound tested was equally effective as ergotamine tartrate in the treatment of migraine and caused less nausea and vomiting than either ergotamine tartrate or acetylsalicylic acid.

Lange R, Schwarz JA, Hohn M. Acetylsalicylic acid effervescent 1000 mg (aspirin) in acute migraine attacks; a multicenter, randomized, double-blind, single-dose, placebo-controlled parallel group study. Cephalalgia 2000 Sep;20(7):663-7.

This was a randomized, double-blind, placebo-controlled, parallel group, multicenter study which compared the effectiveness of a single 1000 mg dose of an effervescent acetylsalicylic acid formulation versus effervescent placebo in the treatment of migraine headache. The study's primary efficacy variable was pain reduction as measured via 4-point categorical scale at 2 hours post ingestion of study medications. In addition, there were 5 secondary efficacy variables listed as follows: the number of migraine attacks that resolved within 2 hours of taking study medication, improvement in associated migraine symptoms (i.e., nausea, vomiting, photophobia, and phonophobia) within the first 2 hours of taking the study medications, the number of recurrent migraine attacks during the first 24 hours post study medications, patients' global drug assessment, and drug-induced side effects. Of the 374 migraine patients who were randomized into the 2 treatment groups, 169 patients treated with effervescent acetylsalicylic acid and 174 patients treated with placebo had sufficient data to be included in the study's efficacy analysis for a total of 343 patients. Analysis of the data generated from the study revealed that 55.0% (93/169 patients) treated with effervescent acetylsalicylic acid reported improvement in the severity of their migraine pain as compared to 36.8% (64/174) treated with placebo. The difference in response rates between the 2 treatment groups for the primary efficacy variable was statistically significant ($p<0.001$). In terms of secondary efficacy variables, a statistically significant difference on comparison of the 2 treatment groups was demonstrated for only 1 of the 5 secondary efficacy variables: the number of migraine attacks that resolved within 2 hours of taking study medication [effervescent acetylsalicylic acid: 29% (49/169) versus placebo: 16.7% (29/174); $p<0.007$]. The group responses to the other 4 secondary efficacy variables were similar and were not shown to be significantly different. (Note: p-values not given.) In terms of safety, 8.3% (14/169) patients from the effervescent acetylsalicylic acid reported a total of 18 adverse events as compared to 2.9% (5/174) of the placebo patients who reported experiencing 9 adverse events during the study. Although the number of adverse events was numerically higher for the effervescent acetylsalicylic acid group the authors state that this difference was not relevant clinically due to the small number of events reported to have occurred in both treatment groups. The most common body system affected for both treatment groups was body as a whole with 5 reported adverse events for the effervescent acetylsalicylic acid group versus 3 for the placebo group. The authors conclude that based on the data generated in this study, effervescent acetylsalicylic acid is a safe and efficacious drug in the treatment of migraine headache.

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