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OTC ANALGESIC-ANTACID COMBINATION PRODUCTS

Nonprescription Drugs Advisory Committee / Drug Safety and Risk Management Advisory Committee Joint Meeting

April 4, 2017

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EXECUTIVE SUMMARY

Bayer HealthCare LLC (Bayer) is a leading innovator and marketer of over-the-counter (OTC) medications for treating a variety of consumer health related complaints and best known for the discovery of aspirin over 120 years ago. Bayer is committed to the development and marketing of products that make a difference in consumers’ lives and diligently assesses the safety of its products on an ongoing basis to ensure their benefit-risk profiles remain favorable. Bayer appreciates the opportunity to participate in the upcoming Nonprescription Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee joint meeting to provide its perspective on the topic of safety issues associated with over-the-counter analgesic-antacid combination products used for upset stomach.

Analgesic-antacid combination products have been available in the US under the Alka-Seltzer brand as effervescent tablets since the 1930’s. These Alka-Seltzer products consist of Monograph recognized antacid ingredients co-formulated with a Monograph recognized analgesic, in this case aspirin (herein referred to as ASA, acetylsalicylic acid). While there are many Alka-Seltzer sub-brands marketed in the US, only three (Alka-Seltzer® Original, Alka-Seltzer® Lemon Lime, and Alka-Seltzer® Extra Strength) are analgesic-antacid combination products and therefore, relevant for the upcoming Advisory Committee meeting. These products are specifically indicated to address dual symptoms of both pain (headache, body aches) and stomach discomfort (heartburn, acid indigestion, sour/upset stomach) that are experienced by many consumers, often in association with overindulgence of food and drink. In addition to the individual components being recognized and labeled according to relevant Monographs, the combination of an analgesic with antacids is also recognized by the current FDA Over Indulgence Tentative Final Monograph (56 FR 66742, FDA, 1991) based on studies on the analgesic-antacid combination available at the time of Monograph review. In addition, a wealth of data supports the utility of the constituent ingredients to induce their desired effects of acid neutralization and pain relief.

Safety has similarly been evaluated in numerous studies for each of the active components in analgesic-antacid combination products. These ingredients have consistently demonstrated a favorable safety profile, exemplified by the low incidence of adverse events in clinical studies as well as in use by tens of millions of people each year for many decades. Importantly, short-term use for self-limiting conditions, as indicated for the products that are the subject of this review, has consistently shown a favorable benefit-risk profile that does not differ appreciably from that of other OTC products.

The use of analgesic-antacid combination products for the treatment of GI symptoms without accompanying pain and/or by individuals at high risk for GI bleeding is inconsistent with the Monograph indications and labeled warnings. This includes the updated stomach warnings promulgated in 2009 to strengthen the labeled warnings on all nonsteroidal anti-inflammatory drug (NSAID)-containing products, including ASA containing analgesic-antacid products, to highlight the increased potential for GI bleeding in those consumers at risk.
As part of its routine pharmacovigilance monitoring, Bayer carefully and continuously evaluates the safety of all its products to assess whether any change to the benefit-risk profile has occurred that may warrant action. These rigorous efforts have continued to confirm the favorable safety profile of the Alka-Seltzer® ASA/antacid combination products. The FDA’s assessment (Drug Safety Communication dated June 6, 2016) cited eight reports of serious GI bleeding events, requiring hospitalization, that had been reported to them since 2009 (the year the revised NSAID warning was introduced). These had occurred in patients with elevated risk for developing serious GI bleeding events. Bayer has received 25 reports containing a serious GI bleeding event since 2010, which includes 5 of the reports cited by FDA. Importantly, during this time-period, there have been over 1.4 billion doses of the Alka-Seltzer® ASA/antacid combination products sold in the US, suggesting the rate of serious GI bleeding is very low (an estimated rate of 1 report/2.4 million users) and may not be distinguishable from the background rate.

Based on a comprehensive review of the available evidence, Bayer concludes the benefit/risk profile for its ASA/antacid combination products remains positive when used according to the product label. Nonetheless, Bayer acknowledges that based on the review of cases of serious GI bleeding, there are instances of possible misuse, and so welcomes the discussion on this monograph topic.

It is important to note that in recent years, the Alka-Seltzer® brand has concentrated its consumer innovation in the US on new products that provide relief focused exclusively on occasional heartburn and upset stomach. These new products align with current consumer interest. Given this shift in consumer preference, as well as to eliminate any potential for consumer misuse, Bayer has made the decision to reformulate its antacid with analgesic products (i.e. Alka-Seltzer® Original, Alka-Seltzer® Lemon Lime, and Alka-Seltzer® Extra Strength) to remove the pain reliever and related indications, focusing exclusively on occasional heartburn and upset stomach relief. Bayer recently communicated this decision to the FDA.
1. ANALGESIC-ANTACID COMBINATION PRODUCTS

1.1. Historical Perspective

1.1.1. Product Origins

Alka-Seltzer® effervescent tablets were first introduced in the 1930s by the Dr. Miles Medicine Company, later named “Miles Laboratories”, which was subsequently purchased by Bayer in 1979. The active principles of the Alka-Seltzer analgesic-antacid combination products are ASA as an analgesic and sodium bicarbonate and citric acid as antacid substances.

Alka-Seltzer® effervescent tablets are currently marketed in 69 countries, with millions of use experiences per year. Three Alka-Seltzer® ASA/antacid combination products in the US contain an analgesic and are therefore included in this Committee’s review: Alka-Seltzer® Original, and Alka-Seltzer® Lemon Lime, Alka-Seltzer® Extra Strength. It should be noted that there are many other products in the Alka-Seltzer line that do not contain an analgesic-antacid combination, and are therefore not addressed further in this document.

1.1.2. Medical Need

Analgesic-antacid combination products fulfill a need for the dual symptomatic relief of both pain (headache/body aches/pains) and GI symptoms (heartburn, acid indigestion, sour/upset stomach). Alka-Seltzer® ASA/antacid combination products combine a fixed dose of sodium bicarbonate and citric acid, substances with rapid acid neutralizing activity, with ASA, an analgesic for short-term and occasional relief of pain. The antacid component helps to alleviate the upset stomach, primarily associated with gastric hyperacidity, while ASA reduces the headache/body aches/pains; a constellation of symptoms that are often associated with overindulgence of food and/or drink (Swift, 1998). Both the pain and GI symptoms are typically self-limiting and consequently, the use of ASA/antacid combination products for symptom relief is short term.

1.2. Product Description

1.2.1. Active Ingredients

Alka-Seltzer® ASA/antacid combination products contain three active ingredients: anhydrous citric acid (antacid), ASA (analgesic), and sodium bicarbonate (antacid). The quantities of each ingredient in the subject products are listed in Table 1.
<table>
<thead>
<tr>
<th>Active Ingredients in each tablet</th>
<th>Alka-Seltzer® Original</th>
<th>Alka-Seltzer® Lemon Lime</th>
<th>Alka-Seltzer® Extra Strength</th>
</tr>
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<tbody>
<tr>
<td>ASA</td>
<td>325 mg</td>
<td>325 mg</td>
<td>500 mg</td>
</tr>
<tr>
<td>Anhydrous Citric acid</td>
<td>1,000 mg</td>
<td>1,000 mg</td>
<td>1,000 mg</td>
</tr>
<tr>
<td>Sodium Bicarbonate</td>
<td>1,916 mg</td>
<td>1,700 mg</td>
<td>1,985 mg</td>
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Directions* - 2 tablets / 4 hours - 2 tablets / 6 hours

*Adults and children 12 years and over

Table 1: Active ingredients of Alka-Seltzer® ASA/antacid combination products

1.2.2. Warnings

Alka-Seltzer® ASA/antacid combination products contain appropriate warnings related to the risks of the product, including the risk of stomach bleeding. These warnings comply with the relevant OTC Drug Monographs regulating these products and are outlined below.

**Warnings**

**Reye's syndrome:** Children and teenagers who have or are recovering from chicken pox or flu-like symptoms should not use this product. When using this product, if changes in behavior with nausea and vomiting occur, consult a doctor because these symptoms could be an early sign of Reye's syndrome, a rare but serious illness.

**Allergy alert:** Aspirin may cause a severe allergic reaction which may include:
- hives
- facial swelling
- asthma (wheezing)
- shock

**Stomach bleeding warning:** This product contains an NSAID, which may cause severe stomach bleeding. The chance is higher if you
- are age 60 or older
- have had stomach ulcers or bleeding problems
- take a blood thinning (antiocoagulant) or steroid drug
- take other drugs containing prescription or nonprescription NSAIDs (aspirin, ibuprofen, naproxen, or others)
- have 3 or more alcoholic drinks every day while using this product
- take more or for a longer time than directed

**Do not use**
- if you are allergic to aspirin or any other pain reliever/fever reducer
- if you have ever had an allergic reaction to this product or any of its ingredients

**Ask a doctor before use if**
- stomach bleeding warning applies to you
- you have a history of stomach problems, such as heartburn
- you have high blood pressure, heart disease, liver cirrhosis, or kidney disease
- you are taking a diuretic
- you have asthma
- you have a sodium-restricted diet

**Ask a doctor or pharmacist before use if you are**
- presently taking a prescription drug, Antacids may interact with certain prescription drugs.
- taking a prescription drug for diabetes, gout, or arthritis

**When using this product do not exceed recommended dosage**
Stop use and ask a doctor if
- an allergic reaction occurs. Seek medical help right away.
- you experience any of the following signs of stomach bleeding
  - feel faint
  - vomit blood
  - have bloody or black stools
- have stomach pain that does not get better
- symptoms get worse or last more than 10 days
- redness or swelling is present
- ringing in the ears or a loss of hearing occurs
- new symptoms occur

If pregnant or breast-feeding, ask a health professional before use. It is especially important not to use aspirin during the last 3 months of pregnancy unless definitely directed to do so by a doctor because it may cause problems in the unborn child or complications during delivery.

Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Table 2: Warnings in the labels of Alka-Seltzer® ASA/antacid combination products

2. REGULATORY

2.1. ASA/Antacid Combination Products in the Monograph

The FDA OTC drug Monograph process was established to evaluate the safety and effectiveness of OTC drug products marketed in the United States before May 11, 1972. OTC drug Monographs are active ingredient-based general regulations that identify acceptable ingredients, dosage forms, labeling, and required testing for each OTC drug class. Products conforming to a Monograph may be marketed without FDA pre-approval, while those that do not must undergo a separate product-specific review and approval via the New Drug Application (NDA) process.

The approved uses of Alka-Seltzer® ASA/antacid combination products are provided for in the FDA Monograph Oration Administered Drug Products for Relief of Symptoms Associated with Overindulgence in Food and Drink for Over-the-Counter Human Use; Tentative Final Monograph. Specifically, this Monograph specifies (56 FR 66742, FDA, 1991):

For the temporary relief of minor aches and pains with” (select one or more of the following: “heartburn,” “sour stomach,” or “acid indigestion”) (which may be followed by: “and upset stomach associated with” (select one or more of the following, as appropriate: “this symptom,” “these symptoms,” “hangover,” or “overindulgence in food and drink”) and “Also may be used for the temporary relief of minor aches and pains alone...

The OTC Alka-Seltzer® ASA/antacid combination products are effervescent dosage formulations comprising ASA, sodium bicarbonate and citric acid. The latter two constituents, both Monograph recognized ingredients (39 FR 19862, FDA, 1974), serve as buffering substances with antacid properties.
Sodium bicarbonate is listed as an antacid in the FDA Monograph Part 33110, *Antacid Products for Over-The-Counter (OTC) Human Use* (39 FR 19862, FDA, 1974). According to this Monograph, it is possible to combine such antacids with other, non-antacid substances:

§ 331.15 Combination with non-antacid active ingredients.
(a)...
(b) An antacid may contain any generally recognized as safe and effective analgesic ingredient(s), if it is indicated for use solely for the concurrent symptoms involved, e.g., headache and acid indigestion, and is marketed in a form intended for ingestion as a solution.

Paragraph (b) applies to Alka-Seltzer® ASA/antacid combination products as they contain sodium bicarbonate and citric acid as well as ASA and are to be dissolved in water prior to oral administration. This Monograph provides the rationale for the traditional use of Alka-Seltzer® ASA/antacid combination products for the so-called dual properties, i.e. the simultaneous treatment of pain and gastrointestinal symptoms.

Another relevant Monograph pertinent to Alka-Seltzer® ASA/antacid combination products is: *Internal Analgesic, Antipyretic and Antirheumatic Drug Products for Over-the-Counter Human Use; Tentative Final Monograph*. This Monograph establishes conditions under which OTC analgesic, antipyretic and antirheumatic drug products, which includes ASA, are generally recognized as safe and effective (53 FR 46204, FDA, 1988).

Overall, these Monographs not only establish safe dose levels, but also include required label text to ensure safe and effective use. Alka-Seltzer® ASA/antacid combination products are in full compliance with the current regulations set forth in the relevant Monographs discussed above.

### 2.2. Stomach Bleeding Warnings

Alka-Seltzer® ASA/antacid combination products carry appropriate warnings related to the risk of stomach bleeding. Bayer has continued to update such statements to comply with continued FDA guidance as it has evolved throughout the development of the *Internal Analgesic* Monograph.

In December 2006, the Agency published a proposed rule regarding the *Internal Analgesic* drug products. It stated that (71 FR 77314 – 77315, FDA, 2006):

...when labeled appropriately and used as directed, (OTC analgesics) are safe and effective OTC drug products that benefit tens of millions of consumers every year. FDA believes that these products should continue to be accessible to consumers in the OTC setting.
However, the Agency acknowledged that new labeling is necessary to ensure consumers know these products can cause stomach bleeding. The new proposed rule therefore included changes to the principle display panel (NSAID must appear highlighted or in bold print) and to the active ingredient section in the Drug Facts Labeling. These statements included an organ specific warning labeled Stomach Bleeding Warning along with revisions to other warning sections listed below. Stomach bleeding warning (71 FR 77334, FDA, 2006):

This product contains a nonsteroidal anti-inflammatory drug (NSAID), which may cause stomach bleeding. The chance is higher if you: • are age 60 or older • have had stomach ulcers or bleeding problems • take a blood thinning (anticoagulant) or steroid drug • take other drugs containing an NSAID (aspirin, ibuprofen, naproxen, or others) • have 3 or more alcoholic drinks every day while using this product • take more or for a longer time than directed.

Ask a doctor before use if you have • stomach problems that last or come back, such as heartburn, upset stomach, or stomach pain • ulcers • bleeding problems • high blood pressure • heart or kidney disease • taken a diuretic • reached age 60 or older.

Ask a doctor or pharmacist before use if you are • taking any other drug containing an NSAID (prescription or nonprescription) • taking a blood thinning (anticoagulant) or steroid drug.

Stop use and ask a doctor if • you feel faint, vomit blood, or have bloody or black stools. These are signs of stomach bleeding. • stomach pain or upset gets worse or lasts more than 10 days

In April 2009, the FDA issued the final rule (75 FR 19385, FDA, 2009) to require the labeling from the 2006 Proposed Rule for OTC Internal Analgesic drug products with minor revisions.

3. EFFICACY

In this section, we provide a brief review of the extensive body of literature that supports the efficacy of Alka-Seltzer® ASA/antacid combination products.

Sodium bicarbonate and citric acid are combined with ASA to create effervescent tablets (i.e. the Alka-Seltzer® ASA/antacid combination products). Upon contact with water, these formulations release carbon dioxide producing the characteristic effervescent action and provide concomitant relief for two symptoms – pain and gastrointestinal discomfort.

3.1. Acid Neutralization

The antacid components of Alka-Seltzer® ASA/antacid combination products (i.e. sodium bicarbonate and citric acid) contribute to the relief of upset stomach, including heartburn, acid indigestion, and sour stomach. The chemical action of the antacid component of Alka-Seltzer®
ASA/antacid combination products help raise the intra-gastric pH level through the removal of hydrogen ions by the anion component of the antacid (neutralization). Dissolution of Alka-Seltzer® ASA/antacid combination tablets in water results in a reaction between the two principle antacid components: sodium bicarbonate and citric acid, releasing carbon dioxide (i.e., the fizz), water and solubilized sodium citrate. Sodium citrate, an effective buffering agent (Washington, 1991), neutralizes hydrochloric acid in the stomach according to the following equation:

$$Na_3C_3H_5O_7 \text{ (sodium citrate)} + 3 \text{ HCl} \rightarrow H_3C_3H_5O_7 \text{ (citric acid)} + 3 NaCl$$

Numerous studies have demonstrated the effectiveness of the acid buffering ingredients included in the Alka-Seltzer® ASA/antacid combination products and are briefly summarized herein. Lange et al. (2000) evaluated the efficacy and safety of an oral effervescent preparation with and without 1000 mg ASA (the dose found in two tablets of Alka-Seltzer® Extra Strength) for the treatment of migraine attacks accompanied by GI symptoms. Both preparations were equally effective in the relief of GI symptoms, supporting the similar effectiveness of the buffering capacity of both preparations. Davison et al. (1962) evaluated 650 mg of ASA/antacid combination in an effervescent form (Alka-Seltzer® ASA/antacid combination) given 15 minutes post prandial to 12 subjects, on gastric acidity and pH. The Alka-Seltzer® ASA/antacid combination significantly reduced free acidity and raised gastric pH (demonstrating acid neutralizing activity) for 30 minutes post ingestion. Chen, et al. (1984) examined the efficacy of Alka-Seltzer® effervescent solution (without ASA) in subjects admitted for emergency surgery when given 5-40 minutes prior to induction of general anesthesia. All subjects in the Alka-Seltzer® effervescent group had a significantly higher gastric juice pH of ≥ 4.0, while more than 80% of the control subjects had a gastric pH ≤ 2.5.

Robinson et al. (2002) compared the efficacy of Alka-Seltzer® effervescent [without ASA] to calcium carbonate in the treatment of gastric hyperacidity. Twenty subjects with a history of episodic heartburn received 1) a solution of Alka-Seltzer® effervescent tablets, 2) swallowable or chewable calcium carbonate tablets [750mg, 1500 mg or 3500 mg] or 3) placebo, one hour after consuming a meal to provoke high gastric acidity/gastro-esophageal reflux (consisting of chili, cheese, raw onions and cola). The onset of action on intra-esophageal pH was similar for all antacids, but only the effervescent bicarbonate solution quickly and significantly increased intragastric pH compared to all other active treatments. The mean 5-minute gastric pH values over the 5.5 hours study period are presented in Figure 1.
Collectively, these studies demonstrate the antacid components of Alka-Seltzer® ASA/antacid combination products effectively reduce gastric acidity through their neutralizing effect on hydrogen ions for at least 40 minutes.

3.2. Pain Relief

In the following sections, we provide a brief summary of the available evidence supporting the analgesic activity of ASA in combination with an antacid and when used alone. Rather than providing a review of the extensive literature supporting the clinical efficacy of ASA, only a few representative studies have been included as examples.

ASA has been used as an analgesic by hundreds of millions of people for nearly 120 years. It is the standard for comparison and evaluation of new analgesic substances, and is one of the most widely studied medications. The efficacy of short-term ASA administration has been demonstrated for the relief of various types of pain, including headache, dental, menstrual, postsurgical, and migraine pain (53 FR 46204, FDA, 1988; Schröer, 2016).

The analgesic effects of ASA follow a dose-response relationship and therapeutic efficacy is affected by inter-individual pharmacokinetic variation. Clinical studies support the effectiveness of ASA as an analgesic at the Monograph recognized doses ranging from 325 to 1,000 mg, and
daily doses of up to 4,000 mg (Edwards, 1999; Yaffee, 1981; 53 FR 46204, FDA, 1988; Schröer, 2016).

### 3.2.1. Mechanism of Action

ASA belongs to the group of acidic non-steroidal anti-inflammatory drugs with analgesic, antipyretic and anti-inflammatory properties. Its mechanism of action is based on irreversible inhibition of cyclo-oxygenase enzymes involved in prostaglandin synthesis. Prostaglandins are mediators of pain and inflammation, with the inhibition of their synthesis resulting in analgesia and a reduction in inflammation (Green, 2001; Vane, 2003; Botting, 2010; Schröer, 2016).

### 3.2.2. Clinical Data

The efficacy studies presented in this section provide support for the use of ASA, primarily alone, for the relief of pain, especially headache, with or without accompanying GI symptoms.

Lange, et al. (2000) evaluated the efficacy of a single dose of oral, buffered (citrate only) effervescent ASA (2 x 500mg) compared to an effervescent placebo for the treatment of acute migraine attack accompanied by GI symptoms. Of the 343 subjects, response rates (reduction of headache severity from severe or moderate to mild or no pain at 2 hours after administration) were 55.0% for the effervescent ASA preparation and 36.8% for placebo (p≤0.001); with 29% of patients in the effervescent ASA preparation group pain-free after 2 hours compared with only 16.7% in the placebo group (P=0.007). The authors concluded an oral effervescent ASA preparation is effective for the combined treatment of acute migraine attacks and accompanying GI symptoms.

Steiner et al. (2003) assessed the analgesic action of a single oral dose of ASA (500 mg and 1,000 mg), and a single oral dose of acetaminophen (500 mg and 1,000 mg) for the treatment of episodic tension-type headache versus placebo. Subjects (n=542; 500 mg ASA: n=111; 1,000 mg ASA: n=103; 500 mg acetaminophen: n=105; 1,000 mg acetaminophen: n=111; placebo: n=112) had a primary headache diagnosis of at least moderate severity with onset of symptoms between 1 hour and 12 hours prior to dosing. The proportion of patients with meaningful or complete headache relief at 2 hours was 70.3% in the 500 mg ASA group, 75.7% in the 1,000 mg ASA group, 63.8% in the 500 mg acetaminophen group, 71.2% in the 1,000 mg acetaminophen group, and 54.5% in the placebo group. Notably, the differences between 500 mg ASA and placebo, as well as between 1,000 mg ASA and placebo were significantly greater in the relief of episodic-type headaches.

Von Graffenried, et al. (1980) conducted a series of studies to evaluate the acute analgesic effect of numerous drugs, including ASA, in patients with non-migraine headache. For ASA, three single dose regimens were tested: 250mg, 500mg and 1,000mg and were found to be significantly
more effective than placebo (see Figure 2 shown below) and demonstrated a significantly
different linear dose-response relationship as compared to placebo.

![Graph showing time-response curves for placebo and three doses of ASA (250mg, 500mg and 1000mg)](image)

**Figure 2: Time-response curves for placebo and three doses of ASA (250mg, 500mg and 1000mg), (Von Graffenried, et al., 1980)**

A 2000 Cochrane Review confirmed that ASA is an effective analgesic for acute pain of moderate
to severe intensity with a clear dose-response (Edwards, 2000). More recently, an update of the
previously published review again concluded that ASA is an effective analgesic for acute pain of
moderate to severe intensity (Derry, 2012). In this latest review, investigators evaluated sixty-
seven studies with 3,111 participants given a single dose of ASA in acute postoperative pain of
moderate to severe intensity versus 2,632 given placebo; most of the studies were based on a
600 mg or 650 mg dose of ASA. The authors concluded “the results confirm that in patients with
moderate to severe postoperative pain, about 40% of those treated with ASA 600/650 mg will
experience good levels of pain relief, compared with about 15% treated with placebo” (Derry,
2012).

### 3.3. Efficacy Conclusions

The efficacy of Alka-Seltzer® ASA/antacid combination products in providing concomitant relief
for symptoms of pain and gastrointestinal discomfort is primarily established through the
evaluation of the individual ingredients, ASA and antacid components (sodium bicarbonate and
citric acid).

Gastric hyperacidity is associated with symptoms of upset stomach: heartburn, acid indigestion,
and sour/upset stomach. As discussed above, numerous studies demonstrate the antacid
components of Alka-Seltzer® ASA/antacid combination products (i.e. sodium bicarbonate and citric acid) help neutralize gastric hydrochloric acid and effectively reduce gastric acidity (as shown by significant increases in gastric pH) as well as associated symptoms.

In addition, there is a large body of evidence that confirms the analgesic activity of 325 – 1000 mg ASA in a broad range of pain types.

Collectively, the data supporting the efficacy of ASA for pain relief and of sodium bicarbonate/citric acid for reducing gastric acidity demonstrate the suitability and effectiveness of the Alka-Seltzer® ASA/antacid combination products. In addition, these products have a long history of use for the relief of symptoms in which consumers complain of both pain (headache/body aches/pains) and GI symptoms (heartburn, acid indigestion, sour stomach), often associated with overindulgence of food and drink; further supporting their effectiveness.

4. SAFETY

When taken short term and as indicated, Alka-Seltzer® analgesic-antacid combination products are very well tolerated and the number of reports of adverse events is low. In addition, the number of reports of serious GI bleeding events has been very low over the marketing history of these products. Likewise, ASA which has been used for close to 120 years, has been consistently shown to have a favorable safety profile suitable for the short-term self-treatment of pain and fever. In addition, ASA safety has been further characterized based on its extensive long-term use in cardiovascular disease management (Baigent et al., 2009; Sutcliffe et al., 2013; Whitlock, 2016).

Numerous clinical studies, as outlined in Section 4.1.1, support the safety of the individual components of effervescent Alka-Seltzer® ASA/antacid combination products. For the combination product, a clinical study by Lange, et al (2000) reported on the safety of buffered effervescent ASA tablets (1000 mg dose) when used for the acute treatment of migraine attack in combination with GI symptoms. Adverse events occurred in 14 of 169 patients (8.3%) of the analgesic-antacid treatment group and were generally mild or moderate and comparable to those of the placebo group (in 5 of 174 patients; 2.9%). No severe adverse events occurred in the active treatment group.

4.1. Gastrointestinal Safety Profile

The gastrointestinal safety concerns related to of Alka-Seltzer® ASA/antacid combination are primarily driven by the ASA component. When used short-term according to label directions, ASA has a favorable safety profile: single doses of 325 -1000 mg with 3,000 to 4,000 mg as a total daily dose (not to exceed 10 days) have been repeatedly demonstrated to be safe and well tolerated. Adverse reactions to ASA, while uncommon with OTC use, are largely GI related and can include both symptomatic complaints as well as mucosal lesions (e.g., erosive gastritis,
gastric ulcer, and gastric bleeding). Symptomatic GI disturbances are manifested most frequently as dyspepsia, heartburn, epigastric distress, or nausea, and less frequently as vomiting, anorexia, or abdominal pain.

GI mucosal injury can result from a combination of direct irritant action on the stomach mucosa as well as an indirect adverse effect on GI homeostasis resulting from COX inhibition. The incidence and severity of these effects are generally dose and duration related. The risk of GI bleeding is very low with OTC use and is most often associated with a history of GI ulcers or bleeding, receiving concomitant therapy with anticoagulants or other NSAIDs, or with concomitant excessive alcohol consumption; all of which are specifically warned against in current NSAID labeling.

4.1.1. Reviews and Clinical Data

In this section, the safety profile of ASA is reviewed. With OTC dosing, GI symptoms mostly include dyspepsia, nausea, vomiting, abdominal discomfort and abdominal pain. Several meta-analyses have assessed the safety of short-term administration of ASA in a variety of self-limiting pain conditions. These analyses have consistently shown that ASA has a favorable safety profile. Notably, the nature, incidence and severity of adverse events reported for ASA in these trials was comparable to that of placebo treatment and/or other comparator analgesics, such as acetaminophen.

Findings from Baron et al. (2013) Meta-Analysis

Baron et al. (2013) conducted a meta-analysis of the published clinical trials to evaluate GI adverse effects of short term use of ASA in both low dose and high dose regimens. Of the 119,310 articles identified, 78 of the highest scoring relevant articles were selected for comparing ASA versus placebo or an active comparator. This analysis included 6712 subjects treated with ASA (2694 [43%] receiving single dose), 3385 placebo, and 9371 an active comparator. ASA was associated with a higher risk of minor GI events relative to placebo or active comparators (ORs were 1.46 [95% CI 1.15–1.86] and 1.81 [95% CI 1.61–2.04], respectively). However, ulcers, perforation, and serious bleeding were not seen from ASA or any of the other interventions. The authors concluded that with short-term use, ASA is associated with a higher frequency of minor GI complaints as compared to other medications commonly used for treatment of pain, colds, and fever. However, no serious adverse events or clinically significant GI bleeding were observed with any ASA or comparators.

Finding from Lanas et al. (2011) Individual Patient Based Data Analysis

Lanas et al. (2011) conducted a safety review and analyzed individual patient data of Bayer-sponsored studies (unpublished and published results herein referred to as Individual Patient Based Data Analysis) of short-term ASA use in acute pain, fever, or common cold. ASA doses in
this meta-analysis were between 325 mg and 4,000 mg per day with 82.5% of subjects receiving single dose ASA; 17.5% multiple-dose; and 3.0% treated for more than 5 days. In total, 13,222 patients from sixty-seven studies were included; 6181 receiving ASA [n = 2298 receiving effervescent form] and 3515 placebo, with the primary endpoints being patient-reported GI AEs. Over half of the subjects (52.3%; 3337 patients) took a daily dose between 500 mg and 1000 mg.

Specifically, for the safety analysis of ASA vs. placebo, a modest increased risk of overall GI adverse events was observed in ASA users (n=4884) in comparison to those receiving placebo (n=3731) (odds ratio 1.3), and particularly dyspepsia (odds ratio 1.7). Pooled incidence rates for GI adverse events were low: 9.9% for ASA, and 9.0% for placebo with no evidence for relevant differences between ASA and acetaminophen or ibuprofen. There was one serious GI AE (GI hemorrhage/hematemesis) reported in the ASA plus dextromethorphan group, and 3 serious GI AE’s in the placebo group (hematemesis, hematochezia and melena). Multiple-dose administration of ASA (up to 5 days) was associated with an increased incidence of AEs (16.2%) when compared with single-dose administration (12.8%) and this was similar to results observed in the placebo arm (17.0% and 12.8%, respectively). These data are summarized in Table 3.

<table>
<thead>
<tr>
<th>Event</th>
<th>ASA arm [%] (n= 4884)</th>
<th>Placebo arm [%] (n= 3731)</th>
<th>OR (95% CI)</th>
<th>Risk difference [%] (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI AEs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All GI AEs</td>
<td>9.9</td>
<td>9.0</td>
<td>1.3 (1.1, 1.5)</td>
<td>2.1 (0.9, 3.3)</td>
</tr>
<tr>
<td>dyspepsia&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.8</td>
<td>1.4</td>
<td>1.7 (1.2, 2.4)</td>
<td>0.8 (0.2, 1.3)</td>
</tr>
<tr>
<td>Minor GI disorders&lt;sup&gt;b&lt;/sup&gt;</td>
<td>5.0</td>
<td>4.5</td>
<td>1.2 (1.0, 1.5)</td>
<td>0.9 (0.0, 1.8)</td>
</tr>
<tr>
<td>abdominal pain&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.5</td>
<td>0.2</td>
<td>1.9 (0.9, 4.0)</td>
<td>0.2 (0.0, 0.5)</td>
</tr>
<tr>
<td>any dyspepsia&lt;sup&gt;d&lt;/sup&gt;</td>
<td>5.3</td>
<td>4.6</td>
<td>1.3 (1.1, 1.6)</td>
<td>1.2 (0.3, 2.2)</td>
</tr>
<tr>
<td>minor dyspepsia&lt;sup&gt;c&lt;/sup&gt;</td>
<td>5.0</td>
<td>4.0</td>
<td>1.4 (1.1, 1.8)</td>
<td>1.5 (0.6, 2.3)</td>
</tr>
<tr>
<td>severe dyspepsia&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.6</td>
<td>0.9</td>
<td>0.7 (0.4, 1.1)</td>
<td>-0.3 (-0.6, 0.1)</td>
</tr>
<tr>
<td>GERD-related symptomsc</td>
<td>&lt;0.1</td>
<td>&lt;0.1</td>
<td>1.5 (0.3, 7.0)</td>
<td>0.03 (-0.09, 0.1)</td>
</tr>
<tr>
<td>Non-GI AEs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>0.8</td>
<td>1.7</td>
<td>0.5 (0.3, 0.8)</td>
<td>-0.7 (-1.2, -0.2)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>0.9</td>
<td>1.1</td>
<td>0.9 (0.6, 1.3)</td>
<td>-0.1 (-0.6, 0.2)</td>
</tr>
<tr>
<td>Tinnitus</td>
<td>0.2</td>
<td>0.1</td>
<td>1.7 (0.6, 4.5)</td>
<td>0.1 (-0.1, 0.3)</td>
</tr>
<tr>
<td>Sign of overdose</td>
<td>1.9</td>
<td>2.8</td>
<td>0.7 (0.6, 1.0)</td>
<td>-0.6 (-1.3, 0.0)</td>
</tr>
<tr>
<td>Other bleeding (non-GI, non cerebral)</td>
<td>0.3</td>
<td>0.2</td>
<td>1.5 (0.6, 3.4)</td>
<td>0.1 (-0.1, 0.3)</td>
</tr>
<tr>
<td>Oral complications&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2.9</td>
<td>3.0</td>
<td>1.3 (0.97, 1.7)</td>
<td>0.6 (-0.1, 1.3)</td>
</tr>
</tbody>
</table>

<sup>a</sup> MedDRA term.
<sup>b</sup> Minor GI disorders include heartburn, nausea, vomiting and abdominal pain. Other terms are defined in table 1.
<sup>c</sup> Combined term.

ASA arm = ASA alone or combined with additional therapy; GERD = gastroesophageal reflux disease; MedDRA = Medical Dictionary for Regulatory Activities; OR = odds ratio; Placebo arm = placebo alone or combined with the additional therapy (pseudoephedrine, lidocaine, or dextromethorphan).

Table 3: Gastrointestinal (GI) adverse events (AEs) and non-GI AEs occurring in patients treated with ASA or placebo

Overall, this safety review of short-term ASA use, mostly single dose and of one-day duration, has shown a low incidence of AEs and a favorable safety profile - at the doses and durations
commonly consumed as OTC medication for the relief of pain, fever, or colds. According to this study, minor gastric problems may be expected with low incidence rates of approximately 5% at most (‘any dyspepsia’), but only one serious GI AE for ASA was reported in the combined meta-analyses presented above which included a total of 12,734 subjects receiving short-term ASA.

**Findings from Bayer’s Bibliographic Database Analysis compared to the Individual Patient Based Data Analysis**

As part of Bayer’s commitment to patient safety, in May 2008 Bayer initiated an internal project to develop a Bibliographic Database (herein referred to as Bibliographic Database Analysis) to evaluate the safety and tolerability of ASA. The database included studies administering short term analgesic therapy in doses of at least 325 mg up to a maximum of 4,000 mg ASA per day for a treatment period <10 days. A meta-analysis was conducted based on data from the manual selection of 4,000 articles from 1918 to 2009, which identified 805 relevant publications providing safety information on short term ASA use compared to placebo and active comparators. In the Bibliographic Database Analysis, safety outcomes included dyspepsia, nausea/vomiting, abdominal pain, perforation, ulcer, and bleeding. Comparisons included ASA (all doses) vs placebo.

After selection of relevant ASA doses and treatment duration, 67 prospective randomized parallel-design studies with 6962 patients contributed to the analysis of ASA versus placebo. Studies previously reported in the Individual Patient Based Data Analysis of Bayer sponsored studies were excluded from this analysis in order to evaluate different populations and thus allow for comparison of results.

For the analysis of ASA vs. placebo, overall occurrence of gastrointestinal adverse events from ASA was consistently reported with an overall incidence rate of about 9% in both the Bibliographic Database Analysis and the Individual Patient Based Data Analysis. Incidences of dyspepsia (minor dyspepsia) and minor GI events after treatment with ASA products were also comparable between Individual Patient Based Data Analysis and Bibliographic Database Analysis (dyspepsia: 5% and 3%, respectively; minor GI events 5% both analyses). Abdominal pain in ASA users was 1% and 3% in these analyses, respectively.

The main difference between the 2 data sets was that the subjects receiving placebo in the studies included in the Bibliographic Database Analysis suffered fewer gastrointestinal adverse events in the categories of GI events, minor GI events and dyspepsia. This might be one of the reasons for higher odds ratios observed in the Bibliographic Database Analysis. Overall, both analyses showed a mildly increased risk to ASA users for gastrointestinal complaints in comparison to placebo. A comparative summary of the data is presented below in Table 4.
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Individual Patient Data Based Analysis</th>
<th>Bibliographic Database Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Incidence ASA (%)</td>
<td>Incidence Placebo (%)</td>
</tr>
<tr>
<td>GI events</td>
<td>9.9</td>
<td>9.0</td>
</tr>
<tr>
<td>Minor GI events</td>
<td>5.0</td>
<td>4.5</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>1.8</td>
<td>1.4</td>
</tr>
<tr>
<td>Nausea / vomiting</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>0.5</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Table 4: Gastrointestinal events (safety outcomes) of Individual Patient Based Data Analysis and Bibliographic Database Analysis - ASA versus placebo

In conclusion, pooled odds ratios observed for ASA in comparison with placebo provided evidence of a mildly elevated risk for ASA users to experience minor GI events including dyspepsia, nausea/vomiting and abdominal pain. Clinically important GI bleeding was observed in only 1 ASA subject, ulcer or perforations were not observed in either meta-analysis of short term use of NSAIDs. These results are generally consistent with the well-documented safety profile for ASA when used for short-term use for relief of pain, fever and the pain symptoms of cold and flu. The results demonstrate a low level of minor GI adverse events, with serious or clinically significant adverse events being very rare.

4.2. Epidemiology of Gastrointestinal Bleedings - Non-ASA Specific

For context, a short overview of the epidemiology of GI bleeding is provided here. Acute gastrointestinal (GI) bleeding is a potentially life-threatening abdominal emergency that remains a common cause of hospitalization. Upper gastrointestinal (UGI) bleeding is defined as bleeding derived from a source proximal to the ligament of Treitz (at the junction of the duodenum and jejunum). The overall incidence in resultant hospitalizations for UGI bleeding declined by over 20% in the first decade of 2001 – 2009. Studies from the early 1990’s indicated hospitalizations for UGI bleeding occurred at an annual incidence of ~100/100,000. However, in 2000 – 2010 the incidence of hospitalizations for UGI bleeding ranged from 85.0/100,000 in 2001 to 66.0/100,000 in 2009 (Laine et al. 2012).

The incidence of UGI bleeding as a component of UGI complications also declined significantly (78.4/100,000 incidence in 2001 to 60.6/100,000 in 2009) (Laine et al. 2012). A large decline in peptic ulcer disease has been attributed to reductions in *H. pylori* prevalence and increases in the use of acid-suppressive medications (Perez-Aisa et al 2005; Lewis J. et al 2002), yet over half the cases of UGI bleeding were due to peptic ulcer disease in 2009. Further supporting this trend, in 2012, 180,767 hospitalizations were reported from Emergency Department visits due to UGI bleeding – a 5% decrease from 2006 (Peery et al 2015). This background rate of GI bleeding
needs to be considered when evaluating the cases of GI bleeding seen with the analgesic-antacid combination products.

4.3. Safety Conclusions

The clinical evidence presented herein supports the safety of the active ingredients in effervescent Alka-Seltzer® ASA/antacid combination products and very rare occurrence of serious GI side effects. In studies that have assessed the safety of short-term ASA treatment for a variety of self-limiting pain types, the adverse event profile reported for ASA was comparable to that of placebo treatment or comparator analgesics. Meta-analyses suggest short-term ASA use is associated with a higher frequency of minor GI complaints as compared to other medications, but not serious bleeding. This well-documented safety profile for ASA use is broadly confirmed by Bayer’s internal monitoring of the safety and tolerability of ASA when used for short-term use for relief of pain.

5. ALKA-SELTZER PHARMACOVIGILANCE

5.1. Pharmacovigilance system

Pharmacovigilance is an important component of Bayer’s commitment to patient safety. The Pharmacovigilance system at Bayer encompasses people, processes and systems that are used to collect, evaluate and report safety data. These data are important in the characterization of the benefit-risk balance for a product. Safety information can come from many sources such as sponsored clinical trials, adverse event reports that are spontaneously received from health professionals or consumers, or the published literature. Bayer’s pharmacovigilance system is in compliance with Good Pharmacovigilance Practices, put forth by Health Authorities worldwide.

As part of its routine pharmacovigilance practice, Bayer monitors the safety data for each product to identify and evaluate new signals to assess whether any change to the benefit-risk profile has occurred and to take appropriate actions as needed. It is important to understand that adverse event reports that are obtained from spontaneous sources have many limitations, and signal detection processes are meant to be hypothesis generating. Therefore, any potential findings are evaluated by employing a systematic process.

Bayer’s Global Pharmacovigilance activities comprise both qualitative and quantitative signal detection methodologies:

- **Qualitative** signal detection is based on medical judgment within defined Pharmacovigilance processes, such as medical review of data from studies, individual case safety reports, scientific literature, and product technical complaints as well as aggregate data review. Additionally, it includes review of data from sources other than Global Pharmacovigilance (e.g. review of pre-clinical studies, HA requests, mass media reports). Qualitative signal detection is performed on an ongoing basis.
Quantitative signal detection is based on defined algorithms and statistical methods applied to the data in the Bayer Global Pharmacovigilance database. These algorithms identify observations that could indicate a possible signal.

Possible signals identified from either qualitative or quantitative detection are medically reviewed, and if a new signal is suspected, an in-depth evaluation is initiated. If, after evaluation, the signal is confirmed, the company takes appropriate action to mitigate the identified risk.

5.2. Adverse Event Reports Summary

5.2.1. General

A summary of the post-marketing reports for ASA/sodium bicarbonate products received by the company for all reports up to December 31, 2016, is presented in Table 5. A total of 5,042 reports were received from the US, and an additional 301 reports from the rest of the world. Sales data from the last 6-year period were used to estimate a recent reporting rate; the estimated reporting rate is 0.99 adverse event reports/million doses sold globally and 2.1 adverse event reports/million doses sold in the US.

The majority of reports, 88% (4677/5343) overall and specifically, 90% (4526/5042) in the US, are categorized as non-serious. Most are spontaneous reports received from consumers. Evaluation of consumer reports can be particularly difficult since these cases often lack important information, despite systematic attempts to obtain follow-up information.

<table>
<thead>
<tr>
<th></th>
<th>US</th>
<th>Ex-US</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Reports</td>
<td>5042</td>
<td>301</td>
<td>5343</td>
</tr>
<tr>
<td>Non-Serious</td>
<td>4526</td>
<td>151</td>
<td>4677</td>
</tr>
<tr>
<td>Serious</td>
<td>516</td>
<td>150</td>
<td>666</td>
</tr>
<tr>
<td>Serious GI Bleeding*</td>
<td>60</td>
<td>81</td>
<td>141</td>
</tr>
</tbody>
</table>

*Reports with a serious event in the Standard MedDRA Query GI hemorrhage

Table 5: Summary of adverse event reports for ASA/sodium bicarbonate products, Cumulative to Dec 31, 2016

Globally, for the non-serious reports, the most frequently reported events include: lack of effect, product use issue, vomiting, unexpected therapeutic response, nausea, no adverse event, unevaluable event, abdominal discomfort and insomnia. In recent years, Bayer has begun to capture issues related to product misuse as MedDRA (Medical Dictionary for Regulatory Activities) terms, in accordance with evolving pharmacovigilance practices. Reports of no adverse event may be associated with an accidental ingestion or misuse of the product that was not accompanied by an untoward event.
Globally, for the serious reports, most frequently reported events include: drug dependence, hematemesis, gastrointestinal hemorrhage, hypersensitivity, dyspnea, myocardial infarction and gastric ulcer. Reports of drug dependence may seem to be unusual. Consumers today often use colloquial terminology such as “I am addicted to this product” to describe a “positive” experience. Such cases, captured from on-line sources with no other information, are coded to dependence, although classical drug dependence is not a safety issue related to these products.

5.2.2. Serious Gastrointestinal Bleeding

As seen in Table 6, in the US, over 17 years, Bayer has received a total of 60 reports containing a serious adverse event term related to gastrointestinal bleeding. Of these reports, 25 were reported between 2010 and 2016. Based upon estimated product sales during this time, this represents an estimated US reporting rate of 1.77 reports /100 million doses sold, or, very conservatively, 1 event reported per 2.4 million users.¹

In 2009 the FDA finalized new labeling language requirements which significantly strengthened the warnings and emphasized the risk of gastrointestinal bleeding for individuals with specific risk factors. While the new labeling was not available in the marketplace instantaneously, it is reasonable to assume that after 2010 most of the product in use reflected the new warning. A comparison of US reports associated with gastrointestinal bleeding before and after the new warnings were introduced is presented below.

<table>
<thead>
<tr>
<th></th>
<th>Jan 1, 1999 to Dec 31, 2009</th>
<th>Jan 1, 2010 to Dec 31, 2016</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious GI Bleeding*</td>
<td>35</td>
<td>25</td>
<td>60</td>
</tr>
<tr>
<td>Reports/year</td>
<td>3.2</td>
<td>3.6</td>
<td>-</td>
</tr>
</tbody>
</table>

* Reports with a serious event in the Standard MedDRA Query GI hemorrhage

Table 6: US adverse event reports of serious GI bleeding for ASA/sodium bicarbonate products, before and after implementation of new warnings

As shown in Table 6, the number of reports received in the US for the products where a serious gastrointestinal bleeding event was cited is relatively consistent over the two-time periods, prior and following the label change.

Over the period from 2010 to 2016, the estimated global reporting rate for the serious events of hematemesis, gastrointestinal hemorrhage and gastric ulcer were 0.25, 0.03, and 0.22 reports/100 million doses, respectively (representing conservatively 17, 136, or 19 million patients treated per reported event, respectively).

¹ Exposure is estimated based upon 1 patient exposure = 46.5 tablets or 23.25 doses
During the period from 2010 to 2016, twenty-five reports of a serious gastrointestinal bleeding event were received by the company. In June 2016 FDA issued a Drug Safety Communication on this issue, and cited 8 reports of a serious bleeding event leading to hospitalization that were associated with use of these products. Bayer reviewed these FDA reports and determined that 5 of the 8 had originated with Bayer, and these are included in the 25 reports discussed herein.

Amongst the 25 reports received by Bayer since the implementation of the new warnings, most were received directly from consumers, and information is typically incomplete, despite attempts to follow-up to obtain more complete data. Some reported events were classified as not related to the use of the product, and/or the temporal relationship to product use was unclear. However, looking closely at these reports, some commonalities come to light. In cases where the consumer specified taking the product for an indication (15/25 reports), ten cited a gastrointestinal indication, such as acid indigestion, without mentioning pain. Also, 7/25 consumers reported taking another analgesic such as another nonsteroidal anti-inflammatory drug in addition to the Alka-Seltzer product. Age was reported in 18 cases; 9 consumers were over age 60.

5.3. Pharmacovigilance Conclusions

Over the years, the company has monitored the safety of the product and these efforts have continued to support the favorable safety profile of the Alka-Seltzer® line, including the ASA/antacid combination products. No new safety signals have been confirmed. The reporting rate for serious GI bleeding remains very low, at an estimated rate of 1 event reported per 2.4 million users, and is consistent from year to year. Among the few consumers in the US who experienced a serious GI bleeding event, some may not have been adhering to all aspects of the labeling. Also, it is not surprising that a product intended to be used to relieve GI symptoms may be associated with a higher GI adverse event rate, due to indication bias. Looking at reports prior to and after implementation of the new, more detailed GI warnings in 2009-2010, there is no substantial difference in the number of reports/year, albeit small, or in the types of events reported.

6. CONCLUSIONS

Alka-Seltzer® ASA/antacid combination products are indicated for the relief of symptoms in which consumers complain of both pain (e.g., headache, body aches) and stomach discomfort (heartburn, acid indigestion, sour/upset stomach). Studies presented in this document confirm the efficacy of ASA (alone or in a buffered effervescent formulation) for the relief of pain with or without accompanying GI symptoms. Likewise, the effectiveness of antacids is not in question.

It is widely recognized that NSAIDs, including ASA, have the potential to disrupt normal GI homeostasis and can, in rare cases, lead to stomach bleeding. As a result, the GI safety of ASA has been extensively studied and the risks well-characterized. These evaluations have
consistently supported its favorable benefit-risk profile. The analgesic-antacid combination products have also demonstrated a favorable safety profile when used as labeled. Furthermore, OTC products containing NSAIDs are labeled to warn consumers regarding the possibility of GI bleeding in at-risk individuals, and these warnings were enhanced in 2009.

Despite these warnings, the FDA has cited a few reports of serious GI bleeding events related to use by individuals with underlying risk factors. In addition, they have noted that the misuse of analgesic-antacid combination products for GI symptoms alone is inconsistent with the Monograph indications and could expose consumers to unnecessary incremental risk. Bayer acknowledges these concerns, but contends that the cases cited by the FDA should be evaluated in the context of the substantial use of these products which suggest that the rate of serious bleeding is remarkably low.

In conclusion, in recent years the Alka-Seltzer® brand has concentrated its consumer innovation in the US on new products that provide relief focused exclusively on occasional heartburn and upset stomach. These new products align with current consumer interest. Given this shift in consumer preference, as well as to eliminate any potential for consumer misuse, Bayer has made the decision to reformulate its antacid with analgesic products (i.e. Alka-Seltzer® Original, Alka-Seltzer® Lemon Lime, and Alka-Seltzer® Extra Strength) to remove the pain reliever and related indications, focusing exclusively on occasional heartburn and upset stomach relief. Bayer recently communicated this decision to the FDA.
REFERENCES


