PRODUCT MONOGRAPH

ADVIL®
HEADACHE CAPLETS

200 mg Ibuprofen Caplets (provided as 256 mg Ibuprofen Sodium Dihydrate)

ADVIL®
HEADACHE TABLETS

200 mg Ibuprofen Tablets (provided as 256 mg Ibuprofen Sodium Dihydrate)

ADVIL®
HEADACHE EXTRA STRENGTH

400 mg Ibuprofen Caplets (provided as 512 mg Ibuprofen Sodium Dihydrate)

Analgesic/Antipyretic

Pfizer Consumer Healthcare, a division of Pfizer Canada Inc.
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Ibuprofen Sodium Dihydrate Caplets

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Caplet(s): 200 mg ibuprofen caplets (provided as 256 mg ibuprofen sodium dihydrate) 400 mg ibuprofen caplets (provided as 512 mg ibuprofen sodium dihydrate) Tablet: 200 mg ibuprofen tablets (provided as 256 mg ibuprofen sodium dihydrate)	None *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

Adults and children 12 years and over:

Advil® Headache (200 mg caplets and tablets and 400 mg caplets provided as ibuprofen sodium 256 mg and 512 mg respectively) are indicated for:

- headache pain including tension headache;
- mild to moderate migraine headaches including associated symptoms of nausea, and sensitivity to light and sound;
- relief of minor aches and pains in muscles, bones and joints, body pain, backache, muscle sprains and strains;
- pain from inflammation associated with conditions including:
  - arthritis
  - physical or athletic overexertion (e.g. sprains or strains);
- menstrual pain (dysmenorrhea);
- toothache (dental pain);
- aches and pains due to the common cold and flu;
- reduction of fever.

Geriatrics (>65 years of age):
Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety or effectiveness. Therefore the use of Advil® Headache in this population is not recommended. (*See Warnings and Precautions and Dosage and Administration*).

Pediatrics (<12 years of age):
Advil® Headache is not indicated for children <12 years of age.

CONTRAINDICATIONS [1,2]

- Active peptic ulcer, a history of recurrent ulceration or active inflammatory disease of the gastrointestinal system.

- Known or suspected hypersensitivity to ibuprofen or other non-steroidal anti-inflammatory drugs. Patients who are hypersensitive to ibuprofen or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph. The potential for cross-reactivity between different NSAIDs must be kept in mind.

- Ibuprofen containing products should not be used in patients with complete or partial syndrome of nasal polyps, or in whom asthma, anaphylaxis, urticarial/angioedema, rhinitis or other allergic manifestations are precipitated by ASA or other nonsteroidal anti-inflammatory agents. Fatal anaphylactoid reactions have occurred in such individuals. As well, individuals with the above medical problems are at risk of a severe reaction even if they have taken NSAIDs in the past without any adverse effects.

- Significant hepatic impairment or active liver disease.

- Severely impaired or deteriorating renal function (creatinine clearance <30 mL/min). Individuals with lesser degrees of renal impairment are at risk of deterioration of their renal function when prescribed NSAIDs and must be monitored.

- Ibuprofen is not recommended for use with other NSAIDs because of the absence of any evidence demonstrating synergistic benefits and the potential for additive side effects.

- Children (i.e. 18 years of age and younger) with kidney disease and children who have suffered significant fluid loss due to vomiting, diarrhea or lack of fluid intake, should not be given ibuprofen.

- Ibuprofen should not be used during pregnancy or by nursing mothers.

- Ibuprofen is contraindicated in patients with systemic lupus erythematosus, as an anaphylaxis-like reaction with fever may occur, particularly when ibuprofen has been administered previously.

- Known hyperkalemia (see Warnings and Precautions - Renal - Fluid and Electrolyte Balance).

- Immediately before or following heart surgery.

- In patients with thyroid disease.

- In patients with Raynaud's Syndrome.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- Use with caution in patients with heart failure, hypertension or other conditions predisposing to fluid retention (See *WARNINGS AND PRECAUTIONS, Cardiovascular and Fluid and Electrolyte Balance; and DRUG INTERACTIONS, Antihypertensives*).
- Caution in patients who might be prone to gastrointestinal tract irritation, particularly those with a history of diverticulosis, including those with a history of peptic ulcer or other inflammatory disease of the gastrointestinal tract such as ulcerative colitis and Crohn's disease (See *WARNINGS AND PRECAUTIONS, Gastrointestinal and DRUG INTERACTIONS, Coumarin-type anticoagulants*).
- Caution in patients at greatest risk of renal toxicity, such as those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and the elderly (*See WARNINGS AND PRECAUTIONS, Renal*).
- If persistent urinary symptoms (bladder pain, dysuria, urinary frequency), hematuria and cystitis occur, the drug should be stopped immediately (See *WARNINGS AND PRECAUTIONS, Genitourinary*).
- Ibuprofen use during pregnancy/nursing should be avoided (*See WARNINGS AND PRECAUTIONS, Special Populations: Pregnant Women and Nursing Women*).

General

As with other anti-inflammatory drugs, ibuprofen may mask the usual signs of infection.

(ADVIL® Headache) is NOT recommended for use with other NSAIDs because of the absence of any evidence demonstrating synergistic benefits and the potential for additive adverse reactions. (See **Drug Interactions - *Drug/Drug Interactions - Acetylsalicylic acid (ASA) or other NSAIDs.***)

Each 200 mg tablet/caplet contains 22 mg of sodium; and each 400 mg caplet contains 44 mg of sodium. This should be taken into consideration in a sodium restricted diet.

Carcinogenesis and Mutagenesis

Not applicable.

Cardiovascular

Use of ibuprofen may precipitate congestive heart failure in patients with marginal cardiac function, elevated blood pressure and palpitations.
Long term continuous use may increase the risk of heart attack or stroke.[87]

Dependence/Tolerance

Not applicable.

Ear/Nose/Throat

Patients with complete or partial syndrome of nasal polyps should not use ADVIL®. See *Contraindications*.

Endocrine and Metabolism
Patients with thyroid disease should not take this drug. See *Contraindications*.

Fluid and Electrolyte Balance
Fluid retention and oedema have been observed in patients treated with ibuprofen. Therefore, as with many other NSAIDs, the possibility of precipitating congestive heart failure in elderly patients or those with compromised cardiac function should be borne in mind. Advil® Headache should be used with caution in patients with heart failure, hypertension or other conditions predisposing to fluid retention.

With nonsteroidal anti-inflammatory treatment there is a potential risk of hyperkalemia, particularly in patients with conditions such as diabetes mellitus or renal failure; elderly patients; or in patients receiving concomitant therapy with B-adrenergic blockers, angiotensin converting enzyme inhibitors or some diuretics. Serum electrolytes should be monitored periodically during long-term therapy, especially in those patients who are at risk.

Gastrointestinal
See *Contraindications*. Serious gastrointestinal (GI) toxicity, such as peptic ulceration, perforation and gastrointestinal bleeding, sometimes severe and occasionally fatal, can occur at any time, with or without symptoms in patients treated with NSAIDs including ibuprofen.

Minor upper GI problems, such as dyspepsia, are common, usually developing early in therapy. Physicians should remain alert for ulceration and bleeding in patients treated with NSAIDs, even in the absence of previous GI tract symptoms.

In patients observed in clinical trials of such agents, symptomatic upper GI ulcers, gross bleeding, or perforation appear to occur in approximately 1% of patients treated for 3-6 months and in about 2-4% of patients treated for one year. The risk continues beyond one year and possibly increases. The incidence of these complications increases with increasing dose.

Advil® Headache should be given under close medical supervision to patients prone to GI tract irritation, particularly those with a history of peptic ulcer, diverticulosis or other inflammatory disease of the gastrointestinal tract such as ulcerative colitis and Crohn's disease. In these cases the physician must weigh the benefits of treatment against the possible hazards.

Physicians should inform patients about the signs and/or symptoms of serious GI toxicity and instruct them to contact a physician immediately if they experience persistent dyspepsia or other symptoms or signs suggestive of GI ulceration or bleeding. Because serious GI tract ulceration and bleeding can occur without warning symptoms, physicians should follow chronically treated patients by checking their haemoglobin periodically and by being vigilant for the signs and symptoms of ulceration and bleeding and should inform the patients of the importance of this follow-up.

If ulceration is suspected or confirmed, or if GI bleeding occurs, Advil® Headache should be discontinued immediately, appropriate treatment instituted and the patient monitored closely.

No studies, to date, have identified any group of patients not at risk of developing ulceration and bleeding. The major risk factors are a prior history of serious GI events and increasing age. Possible risk factors include other factors such as *Helicobacter pylori* infection, excess alcohol intake, smoking, female gender and concomitant oral steroid and anticoagulant, anti-coagulants, anti-platelet agents (including ASA) or selective serotonin reuptake inhibitors (SSRI's) have been associated with increased risk. Studies to date show that all NSAIDs can cause GI tract adverse events. Although existing data does not clearly identify differences in risk between various NSAIDs, this may be shown in the future.

There is no definitive evidence that the concomitant administration of histamine H2-receptor antagonists and/or antacids will either prevent the occurrence of gastrointestinal side effects or allow the continuation of Advil® Headache therapy when and if these adverse reactions appear.

Genitourinary

Some NSAIDs are known to cause persistent urinary symptoms (bladder pain, dysuria, urinary frequency), hematuria or cystitis. The onset of these symptoms may occur at any time after the initiation of therapy with an NSAID. Some cases have become severe on continued treatment. Should urinary symptoms occur, treatment with Advil® Headache must be stopped immediately to obtain recovery. This should be done before any urological investigations or treatments are carried out.

Hematologic

Drugs inhibiting prostaglandin biosynthesis do interfere with platelet function to varying degrees; therefore, patients who may be adversely affected by such an action, such as those on anticoagulants or suffering from haemophilia or platelet disorders, should be carefully observed when ibuprofen is administered. Numerous studies have shown that the concomitant use of NSAIDs and anti-coagulants increases the risk of bleeding. Concurrent therapy with warfarin requires close monitoring of the international normalized ratio (INR). Even with therapeutic INR monitoring, increased bleeding may occur. (See Drug Interactions.)

Blood dyscrasias (such as neutropenia, leukopenia, thrombocytopenia, aplastic anaemia and agranulocytosis) associated with the use of NSAIDs are rare, but could occur with severe consequences.

Hepatic/Biliary/Pancreatic

As with other NSAIDs, borderline elevations of one or more liver function tests (AST, ALT, alkaline phosphatase) may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of more severe hepatic reaction while on therapy with this drug. Severe hepatic reactions including jaundice and cases of fatal hepatitis have been reported with NSAIDs.

Although such reactions are rare, if abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g. eosinophilia, rash, etc.), this drug should be discontinued.

During long-term therapy, liver function tests should be monitored periodically. If there is a need to prescribe this drug in the presence of impaired liver function, it must be done under strict observation.

The frequency of acute liver injury among 625,307 people who received NSAIDs in England and Wales between 1987 and 1991, was examined[4]. There were 311,716 patients who were prescribed ibuprofen. The incidence of acute liver injury among ibuprofen users was 1.6/100,000; this was the lowest incidence among the 8 NSAIDs studied and was significantly lower than the incidence among users of ketoprofen, piroxicam, fenbrufen, or sulindac. For NSAID users as a group, the only factors that had an independent effect on the occurrence of acute liver injury were the simultaneous use of hepatotoxic medication or the presence of rheumatoid arthritis. Based on these data, the short-term use of ibuprofen as an analgesic/antipyretic should not be of concern regarding the development of liver disease.

Immune

Patients with complete or partial syndrome of nasal polyps, rhinitis or other allergic manifestations should not use ASA or other anti-inflammatory agents. Fatal anaphylactoid reactions have occurred in such individuals even if they have taken NSAIDs in the past without any adverse effects (See *Contraindications*).

In occasional cases, with some NSAIDs, the symptoms of aseptic meningitis (stiff neck, severe headaches, nausea and vomiting, fever or clouding of consciousness) have been observed. Patients with autoimmune disorders (systemic lupus erythematosus, mixed connective tissue diseases, etc.) seem to be pre-disposed. Therefore, in such patients, the physician must be vigilant to the development of this complication.

Neurologic

Some patients may experience drowsiness, dizziness, vertigo, insomnia or depression with the use of ibuprofen. If patients experience these side effects, they should exercise caution in carrying out activities that require alertness.

Ophthalmologic
Blurred and/or diminished vision has been reported with the use of ibuprofen and other NSAIDs. If such symptoms develop this drug should be discontinued and an ophthalmologic examination performed; ophthalmic examination should be carried out at periodic intervals in any patient receiving this drug for an extended period of time.

Peri-Operative Considerations
See *Contraindications*. In general, NSAIDs should be discontinued prior to surgeries to decrease the risk of post-operative bleeding[5].

Psychiatric
See *Warnings and Precautions, Neurologic*.

Renal
Long-term administration of NSAIDs to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis with hematuria, proteinuria, and occasionally nephrotic syndrome.

A second form of renal toxicity has been seen in patients with prerenal conditions leading to the reduction in renal blood flow or blood volume, where prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients, administration of a NSAID may cause a dose dependent reduction in prostaglandin formation and may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics, and the elderly. Discontinuation of nonsteroidal anti-inflammatory therapy is usually followed by recovery to the pre-treatment state.

Ibuprofen and its metabolites are eliminated primarily by the kidneys; therefore the drug should be used with great caution in patients with impaired renal function. Those with severely impaired or deteriorating renal function (creatinine clearance <30 mL/min) are at risk. Individuals with lesser degrees of renal impairment are at risk of deterioration of their renal function when prescribed NSAIDs. In these cases, utilisation of lower doses of Advil® Headache should be considered and patients carefully monitored.

During long-term therapy, kidney function should be monitored periodically.

Respiratory
Patients with asthma should not use ASA or other nonsteroidal anti-inflammatory agents. Fatal anaphylactoid reactions have occurred in such individuals even if they have taken NSAIDs in the past without any adverse effects (See *Contraindications*).

Sensitivity/Resistance
Patients sensitive to any one of the NSAIDs may also be sensitive to any of the other NSAIDs.

Sexual Function/Reproduction
Not applicable.

Skin
Serious skin reactions (e.g., exfoliative dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis, and erythema multiforme) can occur in patients receiving NSAIDs. Because the rate of these reactions is low, they have usually been noted during post-marketing surveillance in patients taking other medications also associated with the potential development of these serious skin reactions. Thus, causality is NOT clear. These reactions are potentially life threatening but may be reversible if the causative agent is discontinued and appropriate treatment instituted. These serious skin reactions may occur without warning; patients should be advised to consult their clinician if skin rash and blisters, fever, or other signs of hypersensitivity reaction (e.g., pruritus) occur. NSAIDs should be discontinued at the first appearance of rash or any other sign of hypersensitivity[6]. (Also see *Adverse Reactions, Dermatologic.*)

Special Populations

Pregnant Women: Advil® Headache is contraindicated for use during pregnancy.

Nursing Women: Advil® Headache is contraindicated for use during nursing.

Pediatrics: Advil® Headache is not indicated for children less than 12 years of age.

Geriatrics (> 65 years of age): Patients older than 65 years and frail or debilitated patients are most susceptible to a variety of adverse reactions from NSAIDs: the incidence of these adverse reactions increases with dose and duration of treatment. In addition, these patients are less tolerant to ulceration and bleeding. Most reports of fatal GI events are in this population. Older patients are also at risk of lower oesophageal ulceration and bleeding.

For such patients, considerations should be given to a starting dose lower than the one usually recommended, with individual adjustment when necessary and under close supervision.

Monitoring and Laboratory Tests
For *Warnings and Precautions* related to the use of Advil® Headache and Monitoring and Laboratory Tests see *Fluid and Electrolyte Balance*, *Gastrointestinal*, *Hematologic*, *Hepatic*, *Renal* and *Subpopulations: Elderly*.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Studies of Ibuprofen Sodium Dihydrate[3,7,8,9]

Study AH-09-10, a randomized, double-blind (third party blind), single-center, inpatient, placebo-controlled study was conducted to evaluate the efficacy of a single dose of ibuprofen sodium tablets (ibuprofen 2 x 200 mg, provided as 256 mg ibuprofen sodium dihydrate [equivalent to 400 mg ibuprofen]) in the third molar extraction model of dental pain compared to a single-dose of Advil® tablets (ibuprofen 2 x 200 mg), Motrin IB tablets (ibuprofen 2 x 200 mg) and placebo. The study included subjects 16 to 40 years of age (inclusive).

There were 68 AEs reported by 40 subjects during the study: 8 (16.7%) subjects in the placebo group, 10 (10.5%) subjects in the ibuprofen sodium group, 12 (14.0%) subjects in the Advil® group, and 10 (11.5%) subjects in the Motrin IB group. The majority of AEs were reported in the gastrointestinal disorders system organ class (SOC) with nausea and vomiting being the most frequently reported events. There were 5 (10.4%), 7 (7.4%), 6 (7.0%), and 3 (3.4%) subjects reporting nausea, and 2 (4.2%), 2 (2.1%), 3 (3.5%), and 2 (2.3%) subjects reporting vomiting with placebo, ibuprofen sodium, Advil®, and Motrin IB, respectively. The incidence of individual AEs as well as the overall AEs within each SOC were comparable among all treatments. Except for 4 AEs (that were rated as severe and not related to the study medication: chest discomfort, dyspnea, nausea and vomiting, all in the Advil® tablet group) all AEs were rated as mild or moderate in severity, and with the exception of one AE (nausea, placebo group) all were determined to be not related to study medication. The overall AE incidence rates as well as the individual AE incidence rates within each SOC were comparable among treatments. There were no serious adverse events (SAEs) and no subject discontinued due to AEs. Overall, there were no safety concerns observed and all treatments were well tolerated. Frequent (incidence rate ≥ 2%) treatment-emergent adverse events by SOC and Preferred Term are summarized in Table 1, below.

Table 1: AH-09-10 Frequent (incidence rate ≥ 2%) Treatment-Emergent Adverse Events

SOC Preferred term (MedDRA 13.0)	Placebo (N=48)	Ibuprofen Sodium (N=95)	Advil® (N=86)	Motrin IB (N=87)	Overall P-value[@]
Gastrointestinal disorders					
Nausea	5 (10.4%)	7 (7.4%)	6 (7.0%)	3 (3.4%)	0.409
Vomiting	2 (4.2%)	2 (2.1%)	3 (3.5%)	2 (2.3%)	0.824
Nervous system disorders					
Headache	1 (2.1%)	1 (1.1%)	4 (4.7%)	3 (3.4%)	0.497
Dizziness	1 (2.1%)	1 (1.1%)	3 (3.5%)	3 (3.4%)	0.711
General disorders and administration site conditions					
Feeling hot	2 (4.2%)	1 (1.1%)	0 (0.0%)	2 (2.3%)	0.204
Blood and lymphatic system disorders					
Lymphadenopathy	1 (2.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.152
Ear and labyrinth disorders					
Ear pain	1 (2.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.152
Vascular disorders					
Hypotension	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (2.3%)	0.171
Musculoskeletal and connective tissue disorders					
Pain in extremity	1 (2.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.152

@: p-values are based on the Fisher's exact test.

Study AH-09-14, a randomized, double-blind (third party blind), single-center, inpatient, placebo-controlled study was conducted to evaluate the efficacy of a single dose of ibuprofen sodium tablets (ibuprofen 2 X 200 mg, provided as 256 mg ibuprofen sodium dihydrate [equivalent to 400 mg ibuprofen]) in the third molar extraction model of dental pain compared to a single dose of acetaminophen tablets (Extra Strength Tylenol [acetaminophen]; 2 X 500 mg) and placebo. The study included subjects 16 to 40 years of age (inclusive).

A total of 47 treatment emergent adverse events (AEs) were reported by 26 (11.9%) subjects, with 10 (22.2%) in the placebo group, 5 (5.7%) in the ibuprofen sodium group, and 11 (12.9%) in the acetaminophen group reporting events. There was a significant treatment difference in the overall incidence of AEs (p=0.019), likely due to the higher incidence rate seen with the placebo group. No significant treatment differences were observed in any of the System Organ Classes (SOCs). The incidence of nausea within the gastrointestinal disorder SOC was significantly (p=0.038) different among the 3 treatment groups, where 6 (13.3%) in the placebo group, 2 (2.3%) in the ibuprofen sodium group, and 6 (7.1%) in the acetaminophen group reported this event. The AE rates were not significantly different among the treatment groups for any other individual AE. The majority of AEs were rated as mild or moderate in severity, and none were determined to be related to the study medication. There were no serious adverse event (SAEs) reported in this study, and no subject discontinued due to an AE. Overall, there were no safety concerns and both active treatments were well tolerated. See Table 2 below for an overall summary of adverse events and frequent (incidence rate ≥ 2%) treatment-emergent adverse events by SOC and Preferred Term.

Table 2: AH-09-14 Overall Summary of AEs and Frequent (incidence rate ≥ 2%) AEs

		Placebo N=45	Ibuprofen Sodium 2x256 mg N=88	Acetaminophen 2x500 mg N=85
Incidence Rates by SOC^				
Nervous system disorders	Total n (%)	5 (11.1)	3 (3.4)	9 (10.6)
	Dizziness	1 (2.2)	2 (2.3)	5 (5.9)
	Headache	1 (2.2)	1 (1.1)	3 (3.5)
	Somnolence	1 (2.2)	0 (0.0)	2 (2.4)
	Paraesthesia	1 (2.2)	0 (0.0)	0 (0.0)
	Tremor	1 (2.2)	0 (0.0)	0 (0.0)
Gastrointestinal disorders	Total n (%)	6 (13.3)	3 (3.4)	6 (7.1)
	Nausea	6 (13.3)	2 (2.3)	6 (7.1)
	Vomiting	1 (2.2)	1 (1.1)	2 (2.4)
General disorders and administration site conditions	Total n (%)	1 (2.2)	0 (0.0)	1 (1.2)
	Hyperhidrosis	1 (2.2)	0 (0.0)	1 (1.2)
Musculoskeletal and connective	Total n (%)	1 (2.2)	0 (0.0)	0 (0.0)
	Muscular weakness	1 (2.2)	0 (0.0)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	Total n (%)	1 (2.2)	0 (0.0)	0 (0.0)
	Epistaxis	1 (2.2)	0 (0.0)	0 (0.0)

^Those with incidence rate ≥ 2% in any treatment group

Studies AH-09-11 and AH-11-16 were both randomized, double-blind, placebo-controlled, single-center tension headache studies. In the former, 200 subjects were enrolled and treated with ibuprofen sodium tablets, Motrin IB, or placebo, whereas in the latter, 226 subjects were administered the same treatments. No AEs were reported in either study and no subjects discontinued from either study.

Study AH-09-12, a randomized, multi-center (7 sites, 2 of which did not enroll any subjects), double-blind, placebo-controlled study was conducted to evaluate the antipyretic efficacy of a single dose of ibuprofen sodium tablets (ibuprofen 2 x 200 mg, provided as 256 mg ibuprofen sodium dihydrate [equivalent to ibuprofen 400 mg]) compared to placebo in subjects with an elevated body temperature due to uncomplicated acute viral or bacterial infection. Study AH-09-12 was terminated early due to low recruitment, after 16 of the planned 90 subjects were randomized and received study medication (Na IBU: 9, placebo: 7).

Four subjects (25%) reported a total of six AEs. One subject (14.3%) reported an adverse event following the administration of placebo and 3 subjects (33.3%) reported adverse events following the administration of ibuprofen sodium. The frequencies of AEs by individual preferred term, as well as within each SOC were comparable among all treatment groups. Most AEs were rated as moderate in severity and one was rated severe (cold sweat in the ibuprofen sodium group). Except for one AE (pruritus in the ibuprofen sodium group), all AEs were

determined to be not related to the study treatments. There were no deaths, serious adverse events, or other significant adverse events, and no subject discontinued due to an AE.

Safety Studies of Ibuprofen

One researcher conducted an extensive analysis of published data concerning the relative safety of non-prescription doses of ibuprofen and acetaminophen[10]. Of a total of 96 randomized and blinded trials, there were 10 trials of seven days' duration or less where the safety of both drugs was directly compared. In three of these trials, the incidence of adverse events was higher with acetaminophen; there were no reported adverse events in six trials; and one trial reported a higher incidence with ibuprofen. In this subset of 10 studies, it was reported that gastrointestinal adverse events were found to be the most common type of event reported and were predominantly dyspepsia, nausea, or vomiting. None of the GI events appeared to warrant follow-up from which the author inferred there were no serious gastrointestinal events.

It was concluded: "Although we recognize that the above mentioned data are very selective and are based on information derived from a variety of trial designs and populations, it is nonetheless instructive for indicating a relatively low incidence of severe adverse reactions with both drugs when taken at their respective non-prescription dosages."
The results of a double-blind, placebo-controlled study in healthy subjects (N = 1246) representative of a non-prescription analgesic user population indicate that ibuprofen at a dosage of 1200 mg/day for 10 consecutive days is well tolerated[11]. The frequency of GI Aes was similar in the placebo and ibuprofen groups (16% with placebo vs. 19% with ibuprofen). The most frequent GI Aes (those reported by 1% of the subjects) were dyspepsia, abdominal pain, nausea, diarrhoea, flatulence, and constipation. There was no difference between the two groups in the proportion discontinuing treatment because of GI Aes. Seventeen subjects (1.4%) had positive occult blood tests: the frequency was comparable between the two treatments.

In two multi-trial analyses[12, 13,], a meta analysis[15], and a literature review[10], ibuprofen had a low incidence of GI drug reactions, comparable with that of acetaminophen and placebo.

A large-scale randomized trial comparing non-prescription doses of acetylsalicylic acid, acetaminophen, and ibuprofen in 8677 adults found that the rates of significant adverse reactions were: aspirin 18.7%, ibuprofen 13.7%, and acetaminophen 14.5%[15]. Ibuprofen was not statistically different from acetaminophen. Total GI events (including dyspepsia) and abdominal pain were less frequent with ibuprofen (4% and 2.8%, respectively) than with acetaminophen (5.3% and 3.9%) or aspirin (7.1% and 6.8%) [all $p<0.035$]. It was concluded that "The overall tolerability of ibuprofen in this large-scale study was equivalent to that of paracetamol and better than that of [ASA]."

In epidemiological studies, ibuprofen has consistently exhibited the lowest relative risk of severe gastrointestinal complications compared with other NSAIDs and aspirin[16, 17,18]. No symptom or syndrome emerged in the trials that was not predicted from the drug's pharmacology or could not have been anticipated based on ibuprofen's extensive use as an analgesic/antipyretic in adults.

Garcia-Rodriguez reported on the frequency of acute liver injury among 625,307 people who received NSAIDs in England and Wales between 1987 and 1991, of whom 311,716 were prescribed ibuprofen[4]. The incidence of acute liver injury among ibuprofen users was

1.6/100,000. This was the lowest incidence among the eight NSAIDs studied and was significantly lower than the incidence among users of ketoprofen, piroxicam, fenbufen, or sulindac. For NSAID users as a group, the only factors that had an independent effect on the occurrence of acute liver injury were simultaneous use of hepatotoxic medication and the presence of rheumatoid arthritis (See *Warnings and Precautions, Hepatic/Biliary/Pancreatic*).

Adverse Events with Doses of Ibuprofen ≥1200 mg/day

Note: Reactions listed below under Causal Relationship Unknown are those which occurred under circumstances where a causal relationship could not be established. However, in these rarely reported events, the possibility of a relationship to ibuprofen cannot be excluded.

Gastrointestinal

The adverse reactions most frequently seen with prescribed ibuprofen therapy involve the gastrointestinal system. In clinical trials of NSAIDs, symptomatic upper GI ulcers, gross bleeding, or perforation occurred in approximately 1% of patients treated for 3-6 months and in about 2-4% of patients treated for 1 year. The risk continues beyond 1 year. The incidence of GI complications increases with increasing dose.

Incidence 3-9%: nausea, epigastric pain, heartburn. Incidence 1-3%: diarrhoea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of the GI tract (bloating or flatulence). Incidence <1%: gastric or duodenal ulcer with bleeding and/or perforation, GI haemorrhage, melena, hepatitis, jaundice, abnormal liver function (SGOT, serum bilirubin and alkaline phosphatase).

Allergic

Incidence <1%: anaphylaxis (See *Contraindications*). Causal relationship unknown: fever, serum sickness, lupus erythematosus.

Central Nervous System

Incidence 3-9%: dizziness. Incidence 1-3%: headache, nervousness. Incidence <1%: depression, insomnia. Causal relationship unknown: paraesthesias, hallucinations, abnormal dreams.

Aseptic meningitis and meningoencephalitis, in one case accompanied by eosinophilia in the cerebrospinal fluid, have been reported in patients who took ibuprofen intermittently and did not have any connective tissue disease.

Dermatologic

Incidence 3-9%: rash (including maculopapular type). Incidence 1-3%: pruritus. Incidence <1%: vesiculobullous eruptions, urticaria, erythema multiforme. Causal relationship unknown: alopecia, Stevens-Johnson syndrome.

Cardiovascular

Incidence <1%: congestive heart failure in patients with marginal cardiac function, elevated blood pressure, palpitations. Causal relationship unknown: arrhythmias (sinus tachycardia, sinus bradycardia, palpitations).

Special Senses
Incidence 1-3%: tinnitus. Incidence <1%: amblyopia (blurred and/or diminished vision, scotomata, and/or changes in colour vision). Any patient with eye complaints during ibuprofen therapy should have an ophthalmological examination. Causal relationship unknown: conjunctivitis, diplopia, optic neuritis.

Haematologic
Incidence <1%: leukopenia, decreases in haemoglobin and haematocrit. Causal relationship unknown: haemolytic anaemia, thrombocytopenia, granulocytopenia, bleeding episodes (e.g., purpura, epistaxis, haematuria, menorrhagia).

Hepatic
Incidence less than 1%. Hepatitis, jaundice, abnormal liver function (SGOT, serum bilirubin, and alkaline phosphatase).
Liver enzyme elevations may occur in up to 15% of patients treated with ibuprofen.

Renal
Causal relationship unknown: decreased creatinine clearance, polyuria, azotemia.

Like other non-steroidal anti-inflammatory drugs, ibuprofen inhibits renal prostaglandin synthesis, which may decrease renal function and cause sodium retention. Renal blood flow and glomerular filtration rate decreased in patients with mild impairment of renal function who took 1200 mg/day of ibuprofen for one week. Acute interstitial nephritis with hematuria, proteinuria, and occasionally nephrotic syndrome have been reported. Renal papillary necrosis has been reported. A number of factors appear to increase the risk of renal toxicity (See *WARNINGS AND PRECAUTIONS*).

Endocrine
Causal relationship unknown: gynecomastia, hypoglycaemic reaction. Menstrual delays of up to 2 weeks and dysfunctional uterine bleeding occurred in nine patients taking ibuprofen, 400 mg t.i.d., for three days before menses.

Metabolic
Incidence 1-3%: decreased appetite, oedema, fluid retention.
Fluid retention generally responds promptly to drug discontinuation (See *WARNINGS AND PRECAUTIONS*).

DRUG INTERACTIONS

Serious Drug Interactions

- With acetaminophen may increase the risk of adverse renal effect.
- With acetylsalicylic acid (ASA) or other NSAIDs including ibuprofen, may result in possible additive side effects (See *CONTRAINDICATIONS*).
- With anticoagulants may increase the risk of GI adverse events (*e.g.,* ulceration and bleeding).
- With antihypertensives the benefit and risk must be weighed individually.
- With digoxin may increase serum digoxin concentration and the risk of digoxin toxicity.
- With diuretics may reduce the diuretic effect.
- With hypoglycaemic agents (oral agents and insulin) may increase the risk of hypoglycaemia.
- With lithium may elevate plasma lithium levels, reduce renal lithium clearance and increase the risk of lithium toxicity.
- With methotrexate may increase the risk of methotrexate toxicity.

Overview

Ibuprofen is not recommended for concomitant use with any other NSAIDs, including ASA and other ibuprofen containing products. Documented or possible drug interactions with ibuprofen include acetaminophen, digoxin, anticoagulants, oral antidiabetic agents and insulin, antihypertensives, diuretics, methotrexate, lithium and other protein-bound drugs.

Drug-Drug Interactions

The drugs listed in this section are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (*i.e.,* those identified as contraindicated)[19].

Acetaminophen

Although interactions have not been reported, concurrent use with Advil® Headache is not advisable: it may increase the risk of adverse renal effect.

Acetylsalicylic acid (ASA) or other NSAIDs

The use of Advil® Headache in addition to any other NSAID, including ASA, is not recommended because of the absence of any evidence demonstrating synergistic benefits and the potential for additive side effects. Animal studies show that acetylsalicylic acid given with NSAIDs, including ibuprofen, yields a net decrease in anti-inflammatory activity with lowered blood levels of the non-acetylsalicylic acid drug. Single-dose bioavailability studies in normal

volunteers have failed to show an effect of acetylsalicylic acid on ibuprofen blood levels. Correlative clinical studies have not been conducted (Also see *Contraindications*).
No clinically meaningful loss of cardioprotection was observed, when patients on low dose ASA (81 mg) were administered 400 mg ibuprofen T.I.D.[88], keeping in mind that combination NSAID therapy is associated with additive adverse reactions.

Acetylsalicylic acid (ASA) Low Dose
Ibuprofen can interfere with the anti-platelet effect of low-dose ASA (81 – 325 mg per day). Long-term daily use of ibuprofen may render ASA less effective when used for cardioprotection and stroke prevention. To minimize this interaction, regular users of ibuprofen and low-dose, immediate-release ASA should take the ibuprofen at least one hour after or 11 hours before the daily low-dose ASA. The use of delayed-release (e.g. enteric coated) ASA is not recommended when using ibuprofen regularly. Healthcare professionals should advise consumers and patients regarding the appropriate concomitant use of ibuprofen and ASA.

Antacids
A bioavailability study has shown that there was no interference with the absorption of ibuprofen when given in conjunction with an antacid containing aluminum hydroxide and magnesium hydroxide.[20]

Anticoagulants
Numerous studies have shown that the concomitant use of NSAIDs and anticoagulants increases the risk of GI adverse events such as ulceration and bleeding[21,22]. Because prostaglandins play an important role in hemostasis, and NSAIDs affect platelet function, concurrent therapy of ibuprofen with warfarin requires close monitoring to be certain that no change in anticoagulant dosage is necessary. Several short-term controlled studies failed to show that ibuprofen significantly affected prothrombin time or a variety of other clotting factors when administered to individuals on coumarin-type anticoagulants. Nevertheless, the physician should be cautious when administering Advil® Headache to patients on anticoagulants.

Antihypertensives
Combinations of ACE inhibitors, angiotensin-II antagonists, or diuretics with NSAIDs might have an increased risk for acute renal failure and hyperkalemia. Blood pressure and renal function (including electrolytes) should be monitored more closely in this situation, as occasionally there can be a substantial increase in blood pressure.

Prostaglandins are an important factor in cardiovascular homeostasis and inhibition of their synthesis by NSAIDs may interfere with circulatory control. NSAIDs may elevate blood pressure in patients receiving antihypertensive medication. Two meta analyses have observed this relationship for NSAIDs as a class and for certain NSAIDs in particular, but ibuprofen did not significantly affect blood pressure in either meta analysis.[23,24] Consistent with this lack of effect, a study by Davies et al showed that ibuprofen 1600 mg/day for 14 days did not attenuate the antihypertensive effect of two β-adrenergic blockers.[25] Houston et al showed no effect of three weeks' therapy with ibuprofen on the antihypertensive efficacy of verapamil, but it is not known whether this lack of interaction extends to other classes of calcium channel blockers.[26]

When renal perfusion pressure is reduced both prostaglandins and angiotensin II are important mediators of renal autoregulation[27]. As a class, the combination of an NSAID and angiotensin converting enzyme inhibitor theoretically may have the potential to decrease renal function. One study found a clinically significant decrease in renal function in 4 of 17 patients treated with hydrochlorothioazide and fosinopril who received ibuprofen 2400 mg/day for one month[28]. In contrast, Minuz found no effect on the antihypertensive effect of enalapril or on plasma renin or aldosterone following two days' treatment with ibuprofen 1200 mg/day.[29]

The relationship of ibuprofen and antihypertensives is clearly not well defined. The benefits of concomitant medication should be analysed and compared to the potential risks before being prescribed. If ibuprofen is being recommended for **long-term** use, then periodic monitoring of blood pressure may be useful. Blood pressure monitoring is not necessary if ibuprofen is being recommended for **short-term** use as an **analgesic**.

Digoxin
Ibuprofen has been shown to increase serum digoxin concentration. Increased monitoring and dosage adjustments of digitalis glycoside may be necessary during and following concurrent ibuprofen therapy.[30]

Diuretics
Clinical studies, as well as random observations, have shown that ibuprofen can reduce the natriuretic effect of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis. During concomitant therapy with ibuprofen, the patient should be observed closely for signs of renal failure as well as to assure diuretic efficacy.

Glucocorticoids:
Some studies have shown that the concomitant use of NSAIDs and oral glucocorticoids increases the risk of GI adverse events such as ulceration and bleeding. This is especially the case in older (> 65 years of age) individuals.

H-2 antagonists
In studies with human volunteers, coadministration of cimetidine or ranitidine with ibuprofen had no substantive effect on ibuprofen serum concentrations.[31,32]

Hypoglycaemic Agents
Ibuprofen may increase hypoglycaemic effects of oral antidiabetic agents and insulin.

Lithium
Ibuprofen produced an elevation of plasma lithium levels and a reduction in renal lithium clearance in a study of eleven normal volunteers. The mean minimum lithium concentration increased 15% and the renal clearance of lithium was decreased by 19% during this period of concomitant drug administration. This effect has been attributed to inhibition of renal prostaglandin synthesis by ibuprofen. Thus, when ibuprofen and lithium are administered concurrently, subjects should be observed carefully for signs of lithium toxicity.[33]

Methotrexate
Ibuprofen as well as other NSAIDs has been reported to competitively inhibit methotrexate accumulation in rabbit kidney slices. This may indicate that ibuprofen could enhance the toxicity of methotrexate.[34] Caution should be used when ibuprofen is administered concomitantly with methotrexate.

Selective Serotonin Reuptake Inhibitors (SSRIs) [89, 90]
Studies report an increased risk of gastrointestinal (GI) ulceration and bleeding when Ibuprofen as well as other NSAIDs are taken concomitantly with selective serotonin reuptake inhibitors (SSRIs) than when either class of drugs is taken alone (See Warnings and Precautions – Gastrointestinal).

Other Drugs
Although ibuprofen binds extensively to plasma proteins, interactions with other protein-bound drugs occur rarely. Nevertheless, caution should be observed when other drugs, also having a high affinity for protein binding sites, are used concurrently. No interactions have been reported when ibuprofen has been used in conjunction with probenecid, thyroxine, cyclosporine, antibiotics (e.g. levofloxacin), phenytoin, corticosteroids or benzodiazepines.

Drug-Food Interactions
Interactions with food have not been established.

Drug-Herb Interactions
Interactions with herbs have not been established.

Drug-Laboratory Interactions
Interactions with laboratory tests have not been established.

Drug-Lifestyle Interactions
Avoid drinking alcohol while taking Advil® Headache, as this may increase the risk of serious stomach bleeding. Avoid smoking while taking Advil® Headache or other NSAIDs.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Do not take longer than 3 days for a fever or 5 days for pain unless directed by a physician.

The safety issues to consider when developing a dosage regimen of Advil® Headache for individual patients are applicable to:

- Advil® Headache is not recommended for elderly patients older than 65 years who are frail or debilitated. (See *Warnings and Precautions, Special Populations, Geriatrics*).

Recommended Dose and Dosage Adjustment

Adults and Children 12 years and over: Take 1 (every 4 hours) or 2 (every 6-8 hours) tablets or caplets, or 1 extra strength caplet every 6-8 hours as needed. Do not exceed six tablets or caplets or 3 extra strength caplets in 24 hours, unless directed by a physician.

Missed Dose

Take the missed dose as soon as you remember. If it is almost time for your next dose, wait until then to take your medicine and skip your missed dose. Do not take twice the recommended dose following a missed dose.

Administration

See *Recommended Dose and Dosage Adjustment*.

OVERDOSAGE

Symptoms of Overdosage

The toxicity of overdose is dependent upon the amount of drug ingested and the time elapsed since ingestion; individual responses may vary, thus making it necessary to evaluate each case separately.

Although uncommon, serious toxicity and death have been reported with ibuprofen overdosage. The most frequently reported symptoms of ibuprofen overdose include abdominal pain, nausea, vomiting, lethargy and drowsiness. Other CNS symptoms include headache, tinnitus, CNS depression and seizures. Metabolic acidosis, coma, acute renal failure and apnoea (primarily in very young pediatric patients) may rarely occur. Cardiovascular toxicity, including hypotension, bradycardia, tachycardia and atrial fibrillation, have also been reported.[35-37]

Treatment of Overdosage

In cases of acute overdose, the stomach should be emptied through induction of emesis (in alert patients only) or gastric lavage. Due to the rapid absorption of ibuprofen from the gut, emesis is most effective if initiated within 30 minutes of ingestion. Orally administered activated charcoal may help in reducing the absorption of the drugs when given less than 2 hours following ingestion. There is some evidence that repeated administration of activated charcoal may bind the medication that has diffused from the circulation.[38] Inducing diuresis may be helpful. The treatment of acute overdose is primarily supportive. Management of hypotension, acidosis and GI bleeding may be necessary.

In pediatric patients, the estimated amount of ibuprofen ingested per body weight may be helpful to predict the potential for development of toxicity although each case must be evaluated. Ingestion of less than 100 mg/kg is unlikely to produce toxicity. Pediatric patients ingesting 100 to 200 mg/kg may be managed with induced emesis and a minimal observation time of at least four hours. Pediatric patients ingesting 200 to 400 mg/kg of ibuprofen should have immediate gastric emptying and at least four hours observation. Pediatric patients ingesting greater than 400 mg/kg require immediate medical referral, careful observation and appropriate supportive therapy. Induced emesis is not recommended in overdoses greater than 400 mg/kg because of the risk for convulsions and the potential for aspiration of gastric contents.

In adult patients, the dose reportedly ingested does not appear to be predictive of toxicity. The need for referral and follow-up must be judged by the circumstances at the time of the overdose ingestion. Symptomatic adults should be carefully evaluated, observed and supported.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Examples of Ibuprofen Overdose

A 41-year-old man with multiple medical problems, including long-term renal insufficiency, developed near-fatal acute renal failure after ingestion of a massive dose (36 g) of ibuprofen.[39] He required dialysis for several months, at which point his renal function improved.

With electrolyte replacement and other intensive measures, a 21-month-old child recovered within 5 days after accidental ingestion of 8 g of ibuprofen.[40] A 2-year-old child who ingested approximately 8 g of ibuprofen was treated with activated charcoal, developed metabolic acidosis and acute renal insufficiency, and recovered within 72 hours.[41] A 6-year-old child became comatose after ingesting 6 g of ibuprofen.[42] He was treated with gastric lavage, charcoal, and various supportive measures and recovered within 24 hours.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Like other nonsteroidal anti-inflammatory drugs (NSAIDs), ibuprofen is an analgesic, antipyretic and anti-inflammatory medication.[39] The principal mechanism of action of ibuprofen and other NSAIDs is inhibition of prostaglandin synthesis.[40]

Prostaglandins are naturally occurring fatty acid derivatives that are widely distributed in the tissues. They are believed to be a common factor in the production of pain, fever, and inflammation. Prostaglandins are believed to sensitize tissues to pain- and inflammation-producing mediators such as histamine, 5-hydroxytryptamine, and kinins. The enzyme catalysing the committed step in prostaglandin biosynthesis is prostaglandin endoperoxide synthase, also known as cyclooxygenase. There is significant evidence that the main mechanism of analgesic/antipyretic action of NSAIDs is prostaglandin biosynthesis inhibition.[41] Other pharmacologic effects such as lysosome and plasma membrane stabilisation have been observed, but the potential relevance of these effects to ibuprofen-induced analgesia and antipyresis is unclear.

A recent study has demonstrated that ibuprofen sodium tablets provide a faster onset of analgesia compared to other ibuprofen tablets for relief of dental pain[7]

Pharmacodynamics

At non-prescription dose levels, ≤ 1200 mg daily, the analgesic and anti-pyretic actions prevail, while higher doses are required for full anti-inflammatory action.

Pharmacokinetics

The Advil® Headache formulation (ibuprofen sodium dihydrate) has been shown to be bioequivalent[3] (in terms of overall rate (C_{max}) and extent (AUC_T and $AUC_{Reftmax}$) of ibuprofen absorption) to a currently marketed Advil® Liqui-Gel product containing ibuprofen free acid and potassium salt, and will be labelled with the same maximum daily dosage (i.e., 1200 mg/day). Advil® Headache is expected to have the same pharmacokinetic profile as the currently marketed Advil® Liqui-Gel line of products.

Table 3: Summary of Ibuprofen Sodium Dihydrate's Pharmacokinetic Parameters after a Single 2x256 mg Dose (400 mg of ibuprofen) in Healthy Subjects

	Fasting Conditions	Fed Conditions
AUC_T (µg·h/mL)	145.71 (20.28)	127.21 (22.51)
C_{max} (µg/mL)	50.62 (20.26)	31.49 (27.87)
t_{max} (h)	0.51 (0.33; 1.27)	1.50 (0.52; 6.00)
t½ (h)	2.21 (16.99)	2.65 (37.95)
$AUC_{0-\infty}$ (µg·h/mL)	147.22 (20.41)	130.64 (22.32)
Clearance (L/h)	2.82 (19.56) 2.82 [1.78; 4.16]	3.19 (18.50) 3.27 [1.88; 4.01]
Volume of distribution (L)	8.87 (18.30) 8.78 [6.33; 12.21]	12.03 (40.29) 11.06 [6.46; 34.67]

Data is from 32 subjects dosed in comparative bioavailability Study AH-09-08

AUC_T, C_{max}, $AUC_{0-\infty}$, $t_{1/2}$: Expressed as arithmetic mean (CV%);

t_{max}: Expressed as median (range);

Clearance and Volume of distribution: Expressed as arithmetic mean (CV%) and median [range].

Absorption: Ibuprofen is rapidly and almost completely absorbed. Peak serum concentration occurs within 1-2 hours in adults.[42]

Following a single 400 mg dose of Advil® Headache tablets, peak serum ibuprofen concentration are reached in approximately 31 - 90 minutes.[3] In febrile children ages 3 months to < 12 years, the time of peak serum concentration was 1.60 and 1.54 hours for ibuprofen 5 mg/kg and 10 mg/kg, respectively.[45] Nahata[46] found a time to peak concentration of 1.1 and 1.2 hours for these respective doses. A similar study in febrile children by Walson[47] which used an ibuprofen suspension showed a time of peak serum concentration of 1.3 and 1.7 hours for ibuprofen 5 mg/kg and 10 mg/kg, respectively. Walson also found that mean ibuprofen plasma concentration at one hour was 21.7 ± 6.7 and 28.4 ± 15.2 µg/mL for 5 mg/kg and 10 mg/kg, respectively. Food decreases the rate but not the extent of absorption.[42]

Distribution: The volume of distribution in adults after oral administration is 0.1-0.2 L/kg.[48] In febrile children the volume of distribution is 0.18 and 0.22 L/kg for ibuprofen 5 mg/kg and 10 mg/kg, respectively.[45]

At therapeutic concentrations ibuprofen is highly bound to whole human plasma and to site II of purified albumin.[48] There is no appreciable plasma accumulation of ibuprofen or its metabolites with repeated doses.[42]

Ibuprofen excretion in breast milk following ingestion of one 400 mg ibuprofen tablet every 6 hours for five doses was below the level (i.e., 1µg/mL) of detection.[94] However, a later study using a more sensitive assay showed ibuprofen to be rapidly excreted in breast milk 30 minutes following oral ingestion of 400 mg of ibuprofen at a concentration of 13 ng/mL. A milk: plasma ratio of 1:126 was determined and the exposure of a suckling infant was calculated to be approximately 0.0008% of the maternal dose.[54] It is not known whether ibuprofen crosses the placenta.

Metabolism: Ibuprofen is a racemic mixture of R–(-) ibuprofen and S-(+) ibuprofen. R-(-) ibuprofen undergoes extensive enantiomeric conversion to S-(+) ibuprofen in humans, averaging between 53% and 65%.[43] S-(+) ibuprofen is believed to be the pharmacologically more active enantiomer. Two major metabolites, 2-[4-(2-carboxypropyl)phenyl] propionic acid and 2-[4-(2-hydroxy-2-methylpropyl]propionic acid, have been identified in plasma and urine.[51] The metabolites 1-hydroxyibuprofen and 3-hydroxyibuprofen have also been found in urine in very small concentrations.[91,92] Cytochrome P450 (CYP) 2C9 has been identified as the most important catalyst for formation of all oxidative metabolites of R-(-) and S-(+) ibuprofen.[52] Approximately 80% of a dose is recovered in urine, primarily as carboxymetabolites and conjugated hydroxymetabolites.[48] Ibuprofen does not appear to induce the formation of drug metabolising enzymes in the rat.[51]

Excretion: Ibuprofen's plasma half-life in adults is 1.5-2.0 hours.[49] In febrile children the plasma half-life is 1.65 and 1.48 hours for ibuprofen 5 mg/kg and 10 mg/kg, respectively.[45] Parent drug and metabolites are primarily excreted in the urine; bile and faeces are relatively

minor elimination routes. Total recovery in urine is between 70% and 90% of the administered dose within 24 hours.[48]
There is no evidence of a differential metabolism or elimination of ibuprofen in the elderly. A pharmacokinetic evaluation of ibuprofen in geriatric subjects (65 to 78 years) compared with young adult subjects (22 to 35 years) found that there was no clinically significant difference in the kinetic profiles of ibuprofen for these age groups.[49] Furthermore, there was no statistically significant difference between the two populations in the urinary excretion pattern of the drug and its major metabolites.

The pharmacokinetics of ibuprofen have also been evaluated in children, in whom the metabolism has been shown to be similar to that reported for adults. Walson reported that for ibuprofen 10 mg/kg given to children under 12 years of age, peak plasma concentration occurred at 1.5 hours and then declined with a plasma half-life of 1.8 hours.[95] Thus, ibuprofen appears to exhibit a similar pharmacokinetic profile in all age groups examined.

STORAGE AND STABILITY

Advil® Headache Caplets (200 mg ibuprofen) and Advil® Headache Tablets (200 mg ibuprofen) and Advil® Headache Extra Strength (400 mg ibuprofen caplets) should be stored at room temperature (15-30°C).

Others:
Keep in a safe place out of the reach of children.

SPECIAL HANDLING INSTRUCTIONS

Not applicable.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Advil® Headache Tablets (200 mg ibuprofen tablets) and Advil® Headache Caplets (200 mg ibuprofen caplets)
Advil® Headache 200 mg ibuprofen tablets will be provided as beige-coloured, film-coated tablets, printed with an Advil black ink logo with an asymmetrical underline on one side. The 200 mg ibuprofen tablets contain 256 mg of sodium ibuprofen dihydrate per dosage unit.

Advil® Headache 200 mg ibuprofen caplets will be provided as beige-coloured, film-coated capsule shaped tablets, printed with an Advil black ink logo with an asymmetrical underline on one side. The 200 mg ibuprofen caplets contain 256 mg of sodium ibuprofen dihydrate per dosage unit.

Each beige, film-coated Advil® Headache Caplet and Advil® Headache Tablet contains 200 mg of ibuprofen, provided as 256 mg ibuprofen sodium dihydrate. The caplets are available in blister packages of 10, bottles of 16, 20, 40, 55, 120, 150, 325, 350; and pouches of 1 or 2. The tablets are available in blister packages of 10; bottles of 16, 20, 40, 50, 110, 135, 325, 330; and professional sample pouches of 1 or 2.

The formulation for Advil® Headache Caplets and Advil® Headache Tablets include ibuprofen sodium dihdyrate and the following non-medicinal ingredients:
acesulfame potassium, black iron oxide, caramel colour, carnauba wax, colloidal silicon dioxide, copovidone, hypromellose, mannitol, medium chain triglycerides, microcrystalline cellulose, natural and artificial flavours, polyethylene glycol, propylene glycol, red iron oxide, sodium lauryl sulfate, sucralose, titanium dioxide, yellow iron oxide.

Advil® Headache Extra Strength (400 mg ibuprofen caplets)
Advil® Headache Extra Strength 400 mg ibuprofen caplets will be provided as beige-coloured, film-coated capsule shaped tablets, printed with an Advil 400 black ink logo on one side. The 400 mg ibuprofen caplets contain 512 mg of sodium ibuprofen dihydrate per dosage unit.

Each beige, film-coated Advil® Headache Extra Strength contains 400 mg ibuprofen, provided as 512 mg ibuprofen sodium dihydrate. The caplets are available in blister packages of 10, bottles of 12, 20, 30, 60, 67, 77, 180, and professional sample pouches of 1.

The formulation for Advil® Headache Extra Strength includes ibuprofen sodium dihdyrate and the following non-medicinal ingredients:
acesulfame potassium, black iron oxide, caramel colour, carnauba wax, colloidal silicon dioxide, copovidone, hypromellose, mannitol, medium chain triglycerides, microcrystalline cellulose, natural and artificial flavours, polyethylene glycol, propylene glycol, red iron oxide, sodium lauryl sulfate, sucralose, titanium dioxide, yellow iron oxide.

200 mg Ibuprofen Tablets (Provided as 256 mg Ibuprofen Sodium Dihydrate)	
200 mg Ibuprofen Caplets (Provided as 256 mg Ibuprofen Sodium Dihydrate)	
400 mg Ibuprofen Caplets (Provided as 512 mg Ibuprofen Sodium Dihydrate)	

PART II : SCIENTIFIC INFORMATION

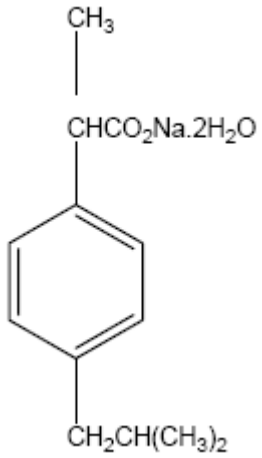
PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Sodium Ibuprofen Dihydrate

Chemical name: Sodium 2-(4-isobutylphenyl)propionate dihydrate

Molecular formula and molecular mass: $C_{13}H_{21}O_4Na$, 264.29



Structural formula:

Physical characteristics: White crystalline powder.

Solubility:

Aqueous Solution	Solubility
Methanol	0.87 g/mL
Ethanol	0.25 g/mL
Acetone	0.001 g/mL
Toluene	Practically insoluble
Ether	Practically insoluble
Water	400-600 mg/mL

pH: A 1% solution in water (pH 4.93) had a pH of 7.32.

Melting Point: 195.3°C

CLINICAL TRIALS [7,8,9]

Studies with Ibuprofen

Published studies have documented the efficacy of 200 mg and 400 mg doses of ibuprofen in treating mild to moderate pain, including sore throat pain[55], headache[56-58], dental pain [59-66], muscle aches[67], and dysmenorrhea[68-73] in adults. The antipyretic efficacy of ibuprofen has been demonstrated at doses of 200 and 400 mg in adults [64, 74-76].

Studies with Ibuprofen Sodium

Two clinical trials in the dental pain model comparing ibuprofen sodium tablets with standard ibuprofen free acid tablets and acetaminophen, two clinical trials in tension headache comparing ibuprofen sodium with standard ibuprofen and placebo, and a fever study comparing ibuprofen sodium with placebo were conducted to support the claims of fast and effective pain and fever relief.

Study demographics and trial design

Study AH-09-10, a randomized, double-blind (third party blind), single-center, inpatient, placebo-controlled study was conducted to evaluate the efficacy of a single dose of ibuprofen sodium tablets (ibuprofen 2 x 200 mg, provided as 256 mg ibuprofen sodium dihydrate [equivalent to 400 mg ibuprofen]) in the third molar extraction model of dental pain compared to a single-dose of Advil® tablets (ibuprofen 2 x 200 mg), Motrin IB tablets (ibuprofen 2 x 200 mg) and placebo. Subjects were evaluated on-site for 8 hours following administration of a single dose of ibuprofen sodium tablets, Advil® tablets, Motrin IB tablets, and placebo following surgical extraction of two or more third molars, at least one of which was required to be a partial or full bony mandibular impaction. Subjects were stratified by baseline categorical pain severity score (moderate or severe) and by gender. Subjective assessments of pain intensity and pain relief using standardized categorical scales were performed at timed intervals for up to 8 hours post-dosing. Times to "first perceptible" relief (FPR) and "meaningful" relief were measured using two stopwatches. Time to rescue medication with an alternate analgesic was recorded if/when it occurred, and a global evaluation was provided by the subjects at 8 hours after dosing (or at the time of rescue medication use, if necessary).

Per protocol, placebo and the three active treatment groups were assigned in a ratio of 1:2:2:2. Three hundred and sixteen (316) subjects were enrolled and received study medication, and were included in the primary ITT population and safety population: 48, 95, 86, and 87 subjects were randomized to the placebo, ibuprofen sodium, Advil® and Motrin IB groups, respectively. The population consisted of 49.1% males and 50.9% females. The majority of the subjects were White (301, 95.3%), followed by other (12, 3.8%), Asian (2, 0.6%), and Black (1, 0.3%). 21 (6.6%) were of Hispanic or Latino ethnicity. The average age was 18.5 years (range: 15-27 years). The treatment groups were comparable with respect to the demographic and baseline characteristics.

Study AH-09-14, a randomized, double-blind (third party blind), single-centre, inpatient, placebo-controlled study was conducted to evaluate the efficacy of a single dose of ibuprofen sodium tablets (ibuprofen 2 x 200 mg, provided as 256 mg ibuprofen sodium dihydrate [equivalent to 400 mg ibuprofen]) in the third molar extraction model of dental pain compared to a single dose of acetaminophen tablets (Extra Strength Tylenol [acetaminophen]; 2 X 500 mg) and placebo.

Subjects were evaluated on-site for 6 hours following administration of a single dose of ibuprofen sodium tablets (ibuprofen 2 x 200 mg, provided as 256 mg ibuprofen sodium dihydrate [equivalent to 400 mg ibuprofen]), APAP (2 x 500 mg) and placebo following surgical extraction of two or more third molars, at least one of which was required to be a partial or full bony mandibular impaction. Subjects were randomly assigned into the placebo and two active treatment groups in a ratio of 1:2:2, respectively and were stratified by baseline categorical pain severity (moderate or severe) and by gender. Subjective assessments of pain intensity and pain relief using standardized categorical scales were performed at timed intervals for up to 6 hours post-dosing. Times to "first perceptible" relief and "meaningful" relief were measured using two stopwatches. Time to rescue medication with an alternate analgesic was recorded if/when it occurred, and a global evaluation was provided by the subjects at 6 hours after dosing (or at the time of rescue medication use, if necessary).

A total of 218 subjects were randomized and received study medication and were included in the intent-to-treat (ITT; [primary]) and safety populations with 45, 88, and 85 subjects in the placebo, ibuprofen sodium, and acetaminophen groups, respectively. The population consisted of 49.5% males and 50.5% females. The majority of the subjects were White (202, 92.7%), followed by other (10, 4.6%), American Indian/Alaskan Native (3, 1.4%), Black (2, 0.9%) and Asian (1, 0.5%). 18 (8.3%) were of Hispanic or Latino ethnicity. The average age was 19.2 years (range: 16-31 years). The treatment groups were comparable with respect to the demographic and baseline characteristics.

Study AH-09-11 was a randomized, double-blind, single center, parallel group, placebo-controlled study conducted to evaluate the analgesic efficacy of a single oral dose of ibuprofen sodium tablets (ibuprofen 2 x 200 mg, provided as 256 mg ibuprofen sodium dihydrate [equivalent to 400 mg ibuprofen]) compared to standard ibuprofen tablets (Motrin IB 2 x 200 mg) and placebo in the treatment of episodic tension headache. Subjects were instructed to return to the study site within 60 minutes of the onset of a tension-type headache, and had eight weeks from study entry to have a qualifying headache episode. Upon arrival at the study site and when the intensity of the headache pain was moderately severe or severe, subjects were randomized and stratified by gender and baseline pain severity (moderately severe or severe pain). Subjects were evaluated on site for three hours following the administration of a single dose of ibuprofen sodium tablets, Motrin IB tablets or placebo.

Subjects were randomized to receive a single dose of study treatment in a 2:2:1 ratio as follows: ibuprofen sodium tablets (ibuprofen 2 x 200 mg, provided as 256 mg ibuprofen sodium dihydrate [equivalent to ibuprofen 400 mg]), standard ibuprofen tablets (Motrin IB 2 x 200 mg) or placebo (2 tablets). Subjects received a single dose of study treatment (4 tablets) as follows: ibuprofen

sodium tablets (2 x 200 mg, provided as 256 mg ibuprofen sodium dihydrate) plus two matching standard ibuprofen placebo tablets; standard ibuprofen tablets (Motrin IB, 2 x 200 mg) plus two matching ibuprofen sodium placebo tablets; or placebo (two matching ibuprofen sodium placebo tablets plus two matching standard ibuprofen placebo tablets). Times to "first perceptible" relief (FPR) and "meaningful" relief were measured using two stopwatches.

Two-hundred subjects were randomized to receive a single treatment of ibuprofen sodium tablets (ibuprofen 2 x 200 mg, provided as 256 mg ibuprofen sodium dihydrate [equivalent to ibuprofen 400 mg]) (N= 79), standard ibuprofen tablets (Motrin IB, 2 x 200 mg) (N= 80), or placebo (N=41). All 200 subjects randomized received treatment and were included in the ITT and safety population; no subjects discontinued from the study.

Of the patients treated with ibuprofen sodium tablets (2 x 200 mg, provided as 256 mg ibuprofen sodium dihydrate), 24 (30.4%) were male and 55 (69.6%) were female; their ages ranged from 18 to 65 years (mean 43.4 years). The demographics of the standard ibuprofen tablets (Motrin IB, 2 x 200 mg) and placebo-treated subjects were similar: 25 were male (31.3%) and 55 (68.8%) were female and their ages ranged from 18 to 63 years (mean 40.9 years) for standard ibuprofen tablets. For placebo-treated subjects, 13 (31.7%) were male and 28 (68.3%) were female, and their ages ranged from 18 to 63 years (mean 42.9 years). The population was nearly all White (97.5%).

Study AH-11-16 was also a randomized, double-blind, single center, parallel group, placebo-controlled study conducted to evaluate the analgesic efficacy of a single oral dose of ibuprofen sodium tablets (2 x 200 mg, provided as 256 mg ibuprofen sodium dihydrate [equivalent to 400 mg ibuprofen]) compared to standard ibuprofen tablets (Motrin IB 2 x 200 mg) and placebo in the treatment of episodic tension headache. Subjects were instructed to return to the study site within 45 minutes of the onset of a tension-type headache, and had eight weeks from study entry to have a qualifying headache episode. Upon arrival at the study site and when the intensity of the headache pain was moderately severe or severe, subjects were stratified by gender and baseline pain severity (moderately severe or severe pain). Subjects were evaluated on site for three hours following the administration of a single dose of ibuprofen sodium tablets, Motrin IB tablets or placebo.

Subjects were randomized to receive a single dose of study treatment in a 2:2:1 ratio as follows: ibuprofen sodium tablets (ibuprofen 2 x 200 mg, provided as 256 mg ibuprofen sodium dihydrate [equivalent to ibuprofen 400 mg]), standard ibuprofen tablets (Motrin IB 2 x 200 mg) or placebo (2 tablets). Subjects received two tablets of study drug, and blinding was maintained by using a third party to administer study drug and by blindfolding subjects during drug administration. Times to "first perceptible" relief (FPR) and "meaningful" relief were measured using two stopwatches.

Two hundred and twenty six (226) subjects were enrolled and received study medication, and were included in the primary ITT and safety population: 46, 91 and 89 subjects were randomized to the placebo, ibuprofen sodium, and Motrin IB groups, respectively. The population consisted of 34.1% males and 65.9% females. The majority of the subjects were White (220, 97.3%),

followed by Black (6, 2.7%). The average age was 42.8 years (range: 18-65 years). The treatment groups were comparable with respect to demographic and baseline characteristics.

Study AH-09-12
This was a multicenter, randomized, double-blind, single-dose, placebo-controlled study performed on patients with fever. The objective of the study was to evaluate the antipyretic efficacy of a single oral dose of ibuprofen sodium tablets (2 x 200 mg, provided as 256 mg ibuprofen sodium dihydrate [equivalent to ibuprofen 400 mg]) compared to placebo.
This trial originally used a naturalistic model evaluating fever associated with upper respiratory/ influenza-like infection; however, due to poor enrollment, the study design was expanded to include fever associated with acute uncomplicated viral and bacterial infections, and the study duration was extended from 12 months to 18 months. After approximately 17 months, the study was closed due to continued slow enrollment.

The study population consisted of male or female subjects, aged 12 to 65 years, experiencing an uncomplicated acute viral or bacterial infection with an oral body temperature of 100ºF (37.8ºC) to 104ºF (40ºC) of 3 days or less duration prior to study enrollment. Eligible subjects were randomized in a 1:1 ratio to receive a single dose of ibuprofen sodium tablets (2 x 200 mg, provided as 256 mg ibuprofen sodium dihydrate [equivalent to ibuprofen 400 mg]) or placebo (2 matching tablets). Baseline temperature was taken within 10 minutes prior to dosing with study medication. From the time the study medication was taken, the duration of evaluation was 2 hours at the center followed by an additional 6 hours on an outpatient basis, for a total evaluation period of 8 hours.

A total of 16 subjects were enrolled and completed the trial; 7 in the placebo group, and 9 in the ibuprofen sodium group. The majority of the enrolled subjects were males (>62%), white (>81%), and between the age of 12 to 65 years (mean 34.8 years). One of the seven subjects (14%) in the placebo group and two of the nine subjects (22%) in the ibuprofen sodium were pediatric subjects (<18 years old). The two treatment groups were balanced in terms of demographic characteristics.

Table 1: Summary of patient demographics for clinical trials in dental, tension headache, and fever models

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
AH-09-10	randomized, double-blind (third party blind), single-center, inpatient, placebo-controlled dental pain study	Ibuprofen 2 x 200 mg, provided as 256 mg ibuprofen sodium dihydrate Ibuprofen tablets 2 x 200 mg (Advil®) Ibuprofen tablets 2 x 200 mg (Motrin IB) Placebo	316	18.5 (15-27)	M – 155 F – 161
AH-09-14	randomized, double-blind (third party blind), single-center, inpatient, placebo-controlled dental pain study	Ibuprofen 2 x 200 mg, provided as 256 mg ibuprofen sodium dihydrate APAP 2 x 500 mg (Extra Strength Tylenol) Placebo	218	19.2 (16-31)	M – 108 F – 110
AH-09-11	randomized, double-blind, single-center, placebo-controlled tension headache study	Ibuprofen 2 x 200 mg, provided as 256 mg ibuprofen sodium dihydrate Ibuprofen tablets 2 x 200mg (Motrin IB) Placebo	200	42.3 (18-65)	M – 77 F - 149
AH-11-16	randomized, double-blind, single-center, placebo-controlled tension headache study	Ibuprofen 2 x 200 mg, provided as 256 mg ibuprofen sodium dihydrate Ibuprofen tablets 2 x 200mg (Motrin IB) Placebo	226	42.8 (18-65)	M – 77 F – 149
AH-09-12	Randomized, double-blind, multiple-center, placebo-controlled fever study	Ibuprofen 2 x 200 mg, provided as 256 mg ibuprofen sodium dihydrate Placebo	16	34.8 (12-65)	M – 10 F – 6

Study Results

AH-09-10

Ibuprofen sodium tablets demonstrated superior overall pain relief compared to placebo over 8 hours and a significantly faster time to meaningful pain relief compared to Motrin IB tablets and Motrin IB and standard Advil® tablets combined (i.e., standard ibuprofen tablets combined), and marginally significantly faster than standard Advil tablets alone (P=0.075). In addition, ibuprofen sodium tablets provided a significantly faster onset of confirmed first perceptible relief compared to all comparators. For the parameters of SPRID, SPID and TOTPAR over 3, 6 and 8 hours Ibuprofen sodium tablets were significantly better than placebo and comparable to the individual ibuprofen tablets (Advil® and Motrin IB). Time to rescue medication was 1.7 hours for placebo compared with > 8 hours for all the ibuprofen-treated groups. Overall, ibuprofen sodium provided better efficacy compared to placebo over 8 hours and faster onset of pain relief compared to standard ibuprofen tablets. The overall efficacy of ibuprofen sodium over the 8 hour study period was comparable to Advil® and Motrin IB tablets.

Table 2: AH-09-10 Summary of Results – Summary of Parameters

	Mean (SD)					P-values			
Parameter	Placebo (n=48)	IBU Na (n=95)	Advil®/Motrin IB Pooled (n=173)	Advil® (n=86)	Motrin IB (n=87)	IBU Na versus PBO	IBU Na versus Advil®/Motrin IB Pooled	IBU Na versus Advil®	IBU Na versus Motrin IB
SPRID 0-8	**5.4 (14.1)**	**29.8 (14.2)**	**31.7 (14.6)**	**31.8 (14.1)**	**31.6 (15.1)**	**<0.001***	**0.323**	**0.361**	**0.434**
Median Time to Meaningful Relief	**>8hrs**	**42.4 min**	**55.3 min**	**52.0 min**	**60.7 min**	**<0.001***	**<0.001***	**0.075**	**<0.001***
SPRID 0-2	1.3 (2.9)	8.0 (3.0)	7.0 (3.3)	7.2 (3.3)	6.8 (3.3)	<0.001*	0.007*	0.058	0.007*
SPRID 0-3	2.1 (4.8)	12.6 (4.7)	11.8 (4.9)	12.1 (4.7)	11.4 (5.1)	<0.001*	0.152	0.493	0.077
SPRID 0-6	4.4 (10.8)	24.3 (10.4)	25.0 (10.6)	25.2 (10.0)	24.8 (11.2)	<0.001*	0.690	0.622	0.847
SPID 0-2	0.1 (1.3)	2.8 (1.4)	2.4 (1.5)	2.5 (1.5)	2.4 (1.5)	<0.001*	0.007*	0.049*	0.008*
SPID 0-3	0.1 (2.1)	4.4 (2.2)	4.1 (2.3)	4.2 (2.3)	4.0 (2.3)	<0.001*	0.144	0.415	0.091
SPID 0-6	0.2 (4.8)	8.5 (4.7)	8.9 (5.0)	8.9 (4.8)	8.9 (5.1)	<0.001*	0.679	0.681	0.764
SPID 0-8	0.1 (6.4)	10.2 (6.3)	11.1 (6.7)	11.1 (6.7)	11.2 (6.8)	<0.001*	0.367	0.438	0.440
TOTPAR 0-2	1.3 (1.8)	5.2 (1.7)	4.6 (1.9)	4.7 (1.8)	4.5 (2.0)	<0.001*	0.009*	0.072	0.007*
TOTPAR 0-3	2.0 (2.9)	8.1 (2.7)	7.6 (2.8)	7.9 (2.6)	7.4 (3.0)	<0.001*	0.166	0.560	0.073
TOTPAR 0-6	4.2 (6.5)	15.9 (6.1)	16.1 (6.1)	16.3 (5.6)	15.9 (6.6)	<0.001*	0.703	0.587	0.909
TOTPAR 0-8	5.2 (8.4)	19.5 (8.5)	20.6 (8.5)	20.7 (8.1)	20.4 (8.9)	<0.001*	0.303	0.320	0.438
Median Time to FPR^ Confirmed by Meaningful Relief	>8 hrs	16.4 min	25.7 min	25.1 min	25.8 min	<0.001*	<0.001*	<0.001*	<0.001*
Median Time to Treatment Failure	1.7 hrs	> 8 hrs	> 8 hrs	> 8 hrs	> 8 hrs	<0.001*	0.281	0.605	0.188
Global Evaluation	1.1 (1.3)	3.8 (1.0)	3.7 (1.2)	3.8 (1.1)	3.6 (1.2)	<0.001*	0.667	0.660	0.226

Note: The two primary parameters/comparisons are bolded.

^ FPR – First perceptible relief

* Significantly better at the 0.05 level

Note: Per protocol the comparisons of Pooled Advil®/Motrin IB versus placebo, and Advil® versus Motrin IB were not performed.

AH-09-14

Ibuprofen sodium tablets (ibuprofen 2 x 200 mg, provided as ibuprofen sodium dihydrate [equivalent to ibuprofen 400 mg]) provided superior analgesic efficacy compared to acetaminophen over the 6 hour evaluation period as shown by SPRID 0-6 (co-primary parameter) and the summary efficacy parameters SPRID, SPID and TOTPAR over 2, 3, and 6 hours, while both active treatments were significantly better than placebo for all these parameters. In addition, ibuprofen sodium was significantly better than acetaminophen and both treatments were better than placebo for the global evaluation of study medication as a pain reliever. Both ibuprofen sodium and acetaminophen provided significantly faster onset of meaningful relief compared to placebo, although the two active treatments were not significantly different from each other. The duration of effect (time to treatment failure) for both active treatments in this study exceeded the 6 hours. Although, both active treatment groups were significantly better than placebo in terms of treatment failure, they were not significantly different from each other. Overall, ibuprofen sodium and acetaminophen provided superior analgesic efficacy compared to placebo over 6 hours. Ibuprofen sodium also demonstrated significantly better overall analgesic efficacy compared to acetaminophen. The two active treatments provided significantly faster onset of pain relief compared to placebo, but were not statistically different from each other.

Both ibuprofen sodium and acetaminophen demonstrated overall analgesic superiority compared to placebo. Ibuprofen sodium also provided significantly better overall analgesic efficacy compared to acetaminophen as demonstrated for both the primary (SPRID 0-6) and secondary summary efficacy endpoints (SPRID, SPID, and TOTPAR over 2, 3, and 6 hours). However, there were no statistically significant differences between the two active treatments for onset of analgesic effect or duration of action. In general, both active treatments were well tolerated.

Table 3 : AH-09-14 Summary of Results for Primary and Key Secondary Parameters

	Mean (SD)			P-values		
Parameter	Placebo (n=45)	IBU Na 2x256 mg (n=88)	APAP 2x500 mg[a] (n=85)	IBU Na vs. PBO	IBU Na vs. APAP	APAP vs. Placebo
SPRID 0-6	**2.8 (9.9)**	**20.0 (11.6)**	**17.1 (11.9)**	**<0.001***	**0.010***	**<0.001[i]**
Median Time to Meaningful Relief	**>6hrs**	**58.0 min**	**53.4 min**	**<0.001***	**0.468**	**<0.001[i]**
SPRID 0-2	0.9 (2.4)	6.9 (3.1)	6.0 (3.3)	<0.001*	0.010*	<0.001*
SPRID 0-3	1.3 (4.2)	10.6 (5.2)	9.1 (5.3)	<0.001*	0.006*	<0.001*
SPID 0-2	-0.1 (1.1)	2.2 (1.4)	1.8 (1.4)	<0.001*	0.007*	<0.001*
SPID 0-3	-0.1 (1.9)	3.4 (2.3)	2.8 (2.1)	<0.001*	0.004*	<0.001*
SPID 0-6	-0.1 (4.4)	6.3 (5.0)	5.1 (4.6)	<0.001*	0.007*	<0.001*
TOTPAR 0-2	0.9 (1.4)	4.7 (1.9)	4.2 (2.0)	<0.001*	0.016*	<0.001*
TOTPAR 0-3	1.4 (2.5)	7.2 (3.1)	6.4 (3.4)	<0.001*	0.010*	<0.001*
TOTPAR 0-6	2.9 (5.9)	13.6 (7.0)	12.0 (7.6)	<0.001*	0.015*	<0.001*
Median Time to FPR[b] Confirmed by Meaningful Relief	>6 hrs	18.0 min	23.7 min	<0.001*	0.323	<0.001*
Median Time to Treatment Failure	1.6 hrs	> 6 hrs	> 6 hrs	<0.001*	0.303	<0.001*
Global Evaluation	0.9 (1.3)	3.5 (1.3)	3.0 (1.5)	<0.001*	0.020*	<0.001*

Note: The two primary parameters are bolded.
a APAP - Acetaminophen tablets (Extra Strength Tylenol)
b FPR – First perceptible relief
* $p \leq 0.05$ in favor of the first treatment listed relative to the second (regardless of technical ineligibilities)
i: $p \leq 0.05$ in favor of the first treatment listed relative to the second but technically ineligible to be declared significant

AH-09-11

In the primary efficacy analysis, there was no significant difference in the SPRID 0-3 scores for ibuprofen sodium compared to placebo (p=0.299). Similarly the SPRID 0-3 scores for the Motrin IB group were not statistically different compared to placebo (p=0.526). There was also no statistically significant difference between the two active groups (p=0.624). Similar results were seen in the time to MR with no statistically significant difference seen between ibuprofen sodium compared to placebo (p=0.304) or between active groups (p=0.193). Treatment with Motrin IB was also not statistically significantly different compared to placebo (p=0.936). Median times to achieve MR was 50.3, 55.5 and 48.2 minutes in the ibuprofen sodium, Motrin IB and placebo groups, respectively. Similar results were also seen in the secondary efficacy analysis, with all three treatment groups not statistically significantly different from each other for any of the parameters.

In general, this study demonstrated a lack of assay sensitivity as neither active treatment was different from placebo. There were no dropouts during the study and no subjects took rescue medication or discontinued due to a lack of efficacy. The large placebo response seen in this study was unexpected, and it is possible that the four-tablet "double-dummy" approach (i.e., two active study medication tablets plus two placebo study medication tablets, or four placebo tablets) may have contributed to the high placebo response due to subjects attributing additional efficacy to the study medications because of the number of tablets (4) administered.

Table 4: AH-09-11 Summary of Primary and Key Secondary Parameters

	Mean (SD)			**P-values**		
Parameter	Placebo (n=41)	IBU Na (n=79)	Motrin IB (n=80)	IBU Na vs. Placebo	Motrin IB vs. Placebo	IBU Na Vs. Motrin IB
SPRID 0-3	**11.2 (4.9)**	**10.8 (5.3)**	**10.2 (5.2)**	**0.299**	**0.526**	**0.624**
Median Time to Meaningful Relief	**48.2 min**	**50.3 min**	**55.5 min**	**0.304**	**0.936**	**0.193**
SPRID 0-2	6.7 (3.1)	6.5 (3.4)	6.1 (3.2)	0.292	0.439	0.733
SPID 0-2	2.2 (1.3)	2.2 (1.3)	2.0 (1.3)	0.259	0.378	0.762
SPID 0-3	3.8 (2.0)	3.6 (2.1)	3.4 (2.2)	0.281	0.582	0.523
TOTPAR 0-2	4.5 (2.0)	4.4 (2.3)	4.1 (2.0)	0.327	0.489	0.726
TOTPAR 0-3	7.5 (3.1)	7.2 (3.5)	6.8 (3.2)	0.320	0.506	0.691
Median Time to FPR[a] Confirmed by Meaningful Relief	42.3 min	41.7 min	43.8 min	0.072	0.652	0.108

Note: The two primary parameters/comparisons are bolded.
[a] Fist Perceptible Relief

AH-11-16

Ibuprofen sodium tablets (ibuprofen, 2 x 200 mg, provided as 256 mg ibuprofen sodium dihydrate [equivalent to ibuprofen 400 mg]) provided superior pain relief compared to placebo and a significantly faster onset of analgesic effect compared to placebo. The results for the 2- and 3-hour summary parameters for SPID, TOTPAR and SPRID were consistent with those for SPRID 0-3 (co-primary parameter) in that ibuprofen sodium and Motrin IB were significantly better than placebo but were not significantly different from each other. The time to MR for ibuprofen sodium was numerically shorter but not significantly different compared to Motrin IB with the pre-specified statistical analysis. However, the post-hoc statistical analysis (Gehan-Wilcoxon test) which assigned higher weights to earlier events showed that ibuprofen sodium provided a faster onset of MR relative to Motrin IB (p=0.022). The significant differences observed between each active treatment compared to placebo in the ITT population were maintained within each baseline pain stratum. However, the subgroup with severe pain at baseline showed a larger numerical separation favoring ibuprofen sodium versus Motrin IB for most parameters, including those relating onset of effect. Within the subgroup with moderately

pain at baseline, the results were consistent with those observed in the overall ITT population. No subject took rescue medication or discontinued due to a lack of efficacy.

Overall, both ibuprofen sodium and Motrin IB provided superior analgesic efficacy compared to placebo over 3 hours, and provided significantly faster onset of pain relief compared to placebo but were not statistically different from each other.

Table 5: AH-11-16 Summary of Primary and Key Secondary Parameters

	Mean (SD)			**P-values**		
Parameter	Placebo (n=46)	IBU Na (n=91)	Motrin IB (n=89)	IBU Na vs. Placebo	Motrin IB vs. Placebo	IBU Na vs. Motrin IB
SPRID 0-3	**3.5 (4.2)**	**9.6 (4.8)**	**9.8 (4.6)**	**<0.001***	**<0.001***	**0.812**
Median Time to Meaningful Relief	**>180 min**	**40.6 min**	**48.5 min**	**<0.001***	**<0.001***	**0.253 (0.022*$)**
SPRID 0-2	1.8 (2.4)	5.5 (2.8)	5.5 (2.8)	<0.001*	<0.001*	0.964
SPID 0-2	0.5 (0.9)	1.7 (1.0)	1.7 (1.0)	<0.001*	<0.001*	0.992
SPID 0-3	1.0 (1.6)	3.0 (1.8)	3.1 (1.6)	<0.001*	<0.001*	0.684
TOTPAR 0-2	1.3 (1.5)	3.8 (1.9)	3.8 (1.9)	<0.001*	<0.001*	0.943
TOTPAR 0-3	2.5 (2.7)	6.6 (3.1)	6.6 (3.0)	<0.001*	<0.001*	0.888
Median Time to FPR [a] Confirmed by Meaningful Relief	>180 min	36.9 min	43.6 min	>0.001*	<0.001*	0.247 (0.018*$)

Note: The two primary parameters are bolded.
a First Perceptible Relief
*: First treatment significantly better than the second at the 0.05 level.
$: p-value based on a post-hoc analysis is reported within parentheses.

AH-09-12

The primary efficacy outcome variable was the time weighted sum of the temperature differences from baseline (hour 0) over 6 hours (STEMPD 0-6). Numerically, results favoured ibuprofen sodium compared to placebo for the primary efficacy variable. However, due to the small sample size of the treatment groups, these differences did not reach statistical significance. The mean±SD STEMPD 0-6 was 10.8 ± 4.9 for the ibuprofen sodium group compared to 3.0 ±6.3 for placebo (p=0.228).

Differences were also seen for the secondary efficacy measures, STEMPD 0-4, STEMPD 0-8 and the subjects' global evaluations of the antipyretic efficacy of the study drug. However, consistent with the primary efficacy analysis, these differences did not reach statistical significance due to the small sample size.

Table 6: AH-09-12: Summary of Efficacy Results

Parameter	Mean ± SD		Treatment Difference (95% CI)[a]	P-value[b]
	Placebo (N=7)	Na IBU (N=9)	Na IBU vs. Placebo	
Primary Efficacy Variable				
STEMPD 0-6	3.0 ± 6.3	10.8 ± 4.9	8.33 (-7.94, 24.60)	0.228
Secondary Efficacy Variables				
STEMPD 0-4	1.7 ± 3.9	6.7 ± 2.9	5.99 (-3.99, 15.97)	0.171
STEMPD 0-8	5.7 ± 9.4	13.4 ± 7.3	8.96 (-14.78, 32.69)	0.354

[a] Treatment difference and associated confidence interval calculated based on least square means
[b] p-values from ANOVA model with treatment and baseline temperature terms except for Global Evaluations where the p values were from the Cochran-Mantel-Haenszel test with modified ridit scores

Comparative Bioavailability Studies[3]

Study AH-09-08, a single-dose, randomized, open-label, in-patient, five-way crossover, comparative bioavailability study was conducted in healthy male and female volunteers (n=36), from 18 - 45 years of age. The rate and extent of ibuprofen absorption following a 400 mg ibuprofen dose from either Advil® Headache (ibuprofen sodium dihydrate tablets) (2x 256 mg; equivalent to 2x 200 mg ibuprofen) or ADVIL® LIQUI-GELS 2x (ibuprofen capsules 200 mg (free acid and potassium salt)) were compared under both fasting and fed conditions. The results of a fifth arm of the study in which Motrin® IB (Ibuprofen Tablets, McNeil Consumer Healthcare Division of Johnson & Johnson Consumer Inc., USA) 200 mg were administered at a dose of 2x200mg in the fasted state are not presented here.

The results from measured data in 32 subjects are summarised in the following tables.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA
FASTING CONDITIONS

Ibuprofen (2 x 256 mg* / 2 x 200) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test[*]	Reference[†]	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (µg·hr/mL)	142.96 145.71 (20.28)	140.69 143.80 (22.64)	102.01	(99.08, 105.03)
AUC_I (µg·hr/mL)	144.42 147.22 (20.41)	142.31 145.50 (22.82)	101.98	(99.05, 104.99)
C_{max} (µg/mL)	49.54 50.62 (20.26)	47.49 48.62 (23.07)	104.17	(96.58, 112.35)
$AUC_{Reftmax}$[€] (µg·hr/mL)	58.5 65.9 (40.2)	49.9 60.3 (46.0)	117.4	90.9 – 151.4
T_{max}[¥] (h)	0.51 (0.33; 1.27)	0.67 (0.42; 3.00)		
$T_{½}$[§] [**] (h)	2.21 (16.99)	2.35 (15.35)		

[*] ADVIL® Headache (ibuprofen sodium dihydrate tablets) (2x256 mg = 2 x 200 mg ibuprofen).
[†]ADVIL® LIQUI-GELS (Ibuprofen Capsules 200 mg (free acid and potassium salt)) (Pfizer Consumer Healthcare, USA) 2 x 200 mg.
[€] AUCReftmax: The area under the curve, for a test product, to the time of the maximum concentration of the reference product, calculated for each study subject.
[¥] Expressed as median [range] only.
[§] Expressed as the arithmetic mean (CV%) only
Note: Source tables label AUC_T as AUC_L

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA
FED CONDITIONS

Ibuprofen (2 x 256 mg* / 2 x 200) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test[*]	Reference[†]	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (µg·hr/mL)	124.50 127.21 (22.51)	122.98 125.86 (23.62)	101.74	(98.83, 104.73)
AUC_I (µg·hr/mL)	127.90 130.64 (22.32)	125.89 128.89 (23.76)	102.13	(99.22, 105.13)
C_{max} (µg/mL)	30.16 31.49 (27.87)	32.81 34.19 (28.33)	91.19	(84.58, 98.33)
$AUC_{Reftmax}$[€] (µg·hr/mL)	23.6 34.7 (66.4)	19.9 35.4 (71.6)	118.5	91.7 – 153.1
T_{max}[¥] (h)	1.50 (0.52, 6.00)	1.50 (0.50, 6.00)		
$T_{½}$[§] [**] (h)	2.65 (37.95)	2.56 (29.18)		

[*] ADVIL® Headache (ibuprofen sodium dihydrate tablets) (2x256 mg = 2 x 200 mg ibuprofen).
[†]ADVIL® LIQUI-GELS (Ibuprofen Capsules 200 mg (free acid and potassium salt)) (Pfizer Consumer Healthcare, USA) 2 x 200 mg.
[€] AUCReftmax: The area under the curve, for a test product, to the time of the maximum concentration of the reference product, calculated for each study subject.
[¥] Expressed as median [range] only.
[§] Expressed as the arithmetic mean (CV%) only
Note: In source table AUCT is presented as AUCL.

Under fasting and fed conditions, ADVIL® HEADACHE (ibuprofen sodium dihydrate tablets) were found to be bioequivalent with respect to both the extent (AUC_T and $AUC_{Reftmax}$) and rate (Cmax) of absorption to ADVIL® LIQUI-GELS (ibuprofen capsules 200 mg (free acid and potassium salt)).

DETAILED PHARMACOLOGY

Animal Pharmacology

After single oral doses of 20 to 150 mg/kg of C^{14} labelled ibuprofen rats, the peak plasma level occurred at or before the earliest time examined (20 minutes in the 20 mg/kg group and 45 minutes in the 150 mg/kg group) and peak levels occurred with 45 minutes of dosing in nearly all tissues examined. The concentration in plasma and tissue decreased to very low levels by six hours after the 20 mg/kg dose and by 17 hours after the 150 mg/kg dose. Sixteen to 38% of the daily dose of ibuprofen was excreted in the urine.[50]

A similar dose was given to dogs for periods of up to six months with no evidence of accumulation of the drug or its metabolites.[50]

Cyclooxygenase inhibitors such as ibuprofen and other NSAIDs reduce thromboxane A_2 production and release, thereby decreasing platelet aggregation.[50] Like many other NSAIDs, ibuprofen inhibits platelet aggregation, as demonstrated in vivo by prevention of platelet disposition in aortopulmonary arterial bypass grafts in dogs.[79] The drug's protective action against pulmonary embolism in rabbits injected intravenously with arachidonic acid may also relate to inhibition of platelet aggregation.[80,81] The decreased platelet aggregation may be due in part to a reduction in membrane fluidity.[82] Ibuprofen may also reduce platelet membrane fluidity, which reduces aggregation[82], but it is not known to what extent TXA_2 synthesis inhibition is involved in this effect.

Human Pharmacology

Two metabolites of ibuprofen were isolated from the urine of patients who had been treated for one month with the drug. The metabolites were identified at 2-4', (2-hydroxy-2-methylpropyl) phenylpropionic acid (metabolite A) and 2-4' (2-carboxpropyl) phenylpropionic acid (metabolite B). About 1/3 of the dose was excreted in the urine of patients as metabolite B, 1/10 as unchanged ibuprofen and 1/10 as metabolite A. The remainder of the dose could not be identified in the urine.[50]

In healthy volunteers, platelet aggregation decreased significantly at a dosage of 1800 mg per day of ibuprofen given over a period of 28 days. Ibuprofen influenced ADP-induced aggregation to a lesser extent than collagen-induced aggregation. Platelet aggregation induced by recalcification of citrated platelet-rich plasma (a thrombin-induced reaction) was not influenced by ibuprofen treatment. Likewise, ibuprofen did not affect whole blood clotting time on recalcification or prothrombin time. Bleeding time measured 2 hours after administration of ibuprofen showed a significant, dose-related increase.

MICROBIOLOGY
Not applicable.

TOXICOLOGY
A single dose rat study was conducted to compare the acute oral toxicities of ibuprofen sodium dihydrate with a USP-grade reference ibuprofen (ibuprofen propionic acid). Five males and five female Sprague-Dawley CD® [Crl:CD®(SD)BR] rats per dose group were dosed by oral gavage once on Day 1 with 200, 500 and 650 mg/kg of ibuprofen sodium or reference ibuprofen. They were then weighed and observed for 14 days. [84]
There was no apparent difference in body weight gains between male and female rats dosed with 200 mg/kg and female rats dosed with 500 mg/kg of both compounds. Male rats dosed with 500 mg/kg reference ibuprofen gained more weight than rats dosed with ibuprofen sodium. There were no weight gain differences for both compounds at the 650 mg/kg dose. [84]

No mortalities were observed in rats dosed at 200 mg/kg with either compound. In the groups dosed with 500 and 650 mg/kg reference ibuprofen, 3 rats were found dead or sacrificed prior to the end of the study. In the groups dosed with 500 and 650 mg/kg ibuprofen sodium, 2 and 7 rats were found dead or sacrificed, respectively. The remainder of the surviving rats were terminated at the study's end. [84]

Tarry feces were observed on Day 1 in all rats dosed at 200 mg/kg with either compound; there were no other significant clinical observations over the 14-day study period. Tarry feces were observed in all animals dosed with both compounds at 500 and 650 mg/kg from Day 1 through to Day 10. There was no appreciable difference in clinical observations or mortality in rats dosed with both compounds. Clinical observations were similar in rats dosed at 650 mg/kg, however, the intensity of observations was more pronounced and frequent in the ibuprofen sodium-dosed animals resulting in 7 mortalities compared to 3 for reference ibuprofen group. Unscheduled necropsies on rats found dead or moribund sacrificed revealed bloated stomach, intestines filled with fluid, serosanguineous fluid in the abdominal cavity, black colored intestinal contents, stomach bleeding and microulcers. These were observed in both 500 and 650 mg/kg doses and compounds. At the highest dose, ibuprofen sodium elicited more toxicity, morbidity and mortality prior to study termination than the reference ibuprofen.[84]

In conclusion, the above study illustrated the known gastrointestinal toxicity of ibuprofen. Equivalent doses of ibuprofen and reference ibuprofen produced similar toxicity profiles. Ibuprofen sodium and reference ibuprofen showed similar toxicity profiles at doses of 200 and 500 mg/kg. There was more mortality and morbidity for ibuprofen sodium at the highest dose of 650 mg/kg. The NOAEL for both compounds was 200 mg/kg, which is 30 times higher than the maximum single human dose. [84]

Further single-dose toxicity studies have been conducted in mice, rats, and dogs with ibuprofen free acid.[50] The LD_{50} values for ibuprofen in mice and rats, expressed as mg/kg of body weight, are as follows:

Mice	Oral	800 mg/kg
	Intraperitoneal	320 mg/kg
Rats	Oral	1600 mg/kg
	Subcutaneous	1300 mg/kg

Acute signs of poisoning were prostration in mice and sedation, prostration, loss of righting reflex, and laboured respiration in rats. Death occurred within 3 days from perforated gastric ulcers in mice and intestinal ulceration in rats, irrespective of the route of administration. Single ibuprofen doses of 125 mg/kg and above in dogs caused emesis, transient albuminuria, faecal blood loss, and erosions in the gastric antrum and pylorus. No ill effects were seen with doses of 20 or 50 mg/kg.

The primary toxic effect of ibuprofen in repeated doses in rats is intestinal damage.[50] At a dosage of 180 mg/kg/day for 26 weeks, ibuprofen alters the organ-to-body weight ratio of certain organs, such as the liver, kidneys, gonads, and secondary sex organs, although no histological abnormalities have been observed and the effects are reversible. The liver and kidney enlargement may be a reflection of work hypertrophy associated with the metabolism and excretion of the compound, whereas the significance of the effects on other organs is unknown. When administered in lethal doses (540 mg/kg/day), ibuprofen produces mild kidney lesions in addition to intestinal damage.

In rats given 180 mg/kg/day of ibuprofen orally for 55 weeks and 60 mg/kg/day for the next 60 weeks, the only specific pathological effect observed was intestinal ulceration.[85] There was no evidence of tumour induction, indicating that ibuprofen is not carcinogenic in rats. Ibuprofen is not teratogenic when given in toxic doses (60 mg/kg/day) to rabbits or in ulcerogenic doses (180 mg/kg/day to rats.[50]

Carcinogenic Potential
Thirty male and thirty female rats were given 180 mg/kg/day of ibuprofen orally for 55 weeks and 60 mg/kg/day for the next 60 weeks. The only specific pathological effect observed was intestinal ulceration. There was no evidence of tumour induction and it is concluded that ibuprofen is not carcinogenic in the rat.[85]

Teratology Study in Rabbits
New Zealand white rabbits were given 0, 7.5, 20 and 60 mg/kg daily of ibuprofen from day 1 to day 29 of pregnancy. The mean fetal weight was unaffected; litter size was unaffected at the lower doses. Congenital malformations did occur in both treated and untreated groups with no consistent pattern except for one litter of 4 young with cyclopia. The results of this experiment indicate that ibuprofen is not teratogenic when given in toxic doses to rabbits.[50]

Teratology Study in Rats
Newly-mated female albino rats were given ibuprofen in doses of 0, 7.5, 20, 60 and 180 mg/kg/day from day 1 to day 20 of pregnancy; ibuprofen exhibited no embryotoxic or teratogenic effects even when administered at ulcerogenic doses.[50]

Penetration of Ibuprofen into the Rabbit and Rat Fetus
The penetration of ibuprofen into rabbit and rat foetuses was investigated. Rabbits and rats in late pregnancy were given single oral doses of 60 and 20 mg/kg respectively of C^{14}-labeled ibuprofen.[93] Rabbits were killed 3 hours after dosing, and rats were killed 1.5 hours after dosing. Blood samples were collected from the mothers and foetuses. The concentrations of radioactively labelled material were similar in maternal and foetal blood, indicating that ibuprofen and its metabolites readily crossed the placenta and entered the foetal circulation.

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PART III: CONSUMER INFORMATION

Advil® Headache Caplets (200 mg ibuprofen caplets, provided as 256 mg ibuprofen sodium dihydrate)

This leaflet is part III of a three-part "Product Monograph" published when Advil® Headache Caplets was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Advil® Headache Caplets. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
Fast and effective relief of headache including tension headache, toothache, menstrual pain, minor aches and pain associated with muscles, bones and joints, sprains and strains, backache, body pain, pain from inflammation associated with arthritis or physical overexertion,, and aches and pains due to the common cold and flu, in addition to reducing fevers.

Advil® Headache Caplets also provide temporary relief of mild to moderate migraine headaches including associated symptoms of nausea, and sensitivity to light and sound.

Provides up to 8 hours of long lasting pain relief.

What it does:
Ibuprofen sodium reduces pain and fever.

When it should not be used:
Do not use Advil® Headache Caplets if you have or are:
- allergic/hypersensitive to acetylsalicylic acid (ASA), ibuprofen, other salicylates, other non-steroidal anti-inflammatory drugs (NSAIDs) or any of Advil® Headache Caplet's ingredients (Refer to the nonmedicinal ingredients section of this insert),
- peptic ulcer disease, gastrointestinal bleeding or active inflammatory bowel disease (e.g. Crohn's, colitis) ,
- taking ASA or other NSAIDs including any other ibuprofen product,
- nasal polyps (swelling of the inside of the nose),
- asthma,
- allergic manifestations such as anaphylaxis (sudden severe life threatening allergic reaction), urticaria/hives, rhinitis (stuffed or runny nose that may be due to allergies), skin rash or other allergic symptoms,
- dehydrated (significant fluid loss) due to vomiting, diarrhea or lack of fluid intake,
- been diagnosed with severe high blood pressure or have heart disease,
- about to have or just had heart surgery,
- serious liver disease,
- severe kidney disease,
- thyroid disease,
- Raynaud's Syndrome (a disorder of the circulatory system),
- Systemic Lupus Erythematosus,
- pregnant or nursing.

What the medicinal ingredient is:
Ibuprofen sodium dihydrate.

What the important nonmedicinal ingredients are:
acesulfame potassium, black iron oxide, caramel colour, carnauba wax, colloidal silicon dioxide, copovidone, hypromellose, mannitol, medium chain triglycerides, microcrystalline cellulose, natural and artificial flavours, polyethylene glycol, propylene glycol, red iron oxide, sodium lauryl sulfate, sucralose, titanium dioxide, yellow iron oxide.

What dosage forms it comes in:
Advil® Headache Caplets contain ibuprofen 200 mg, provided as 256 mg ibuprofen sodium dihydrate.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- **Caution in patients with heart failure, high blood pressure or other conditions predisposing to fluid retention.**
- **Caution in patients at risk of gastrointestinal tract irritation.**
- **Caution in those at risk of kidney or liver problems, those taking diuretics and the elderly.**
- **Stop use immediately if you have difficulty or pain when urinating.**

BEFORE you use Advil® Headache Caplets talk to your doctor or pharmacist if you have:
- blood clotting disorder (such as hemophilia),
- breathing problems or chronic lung disease (such as chronic bronchitis),
- diabetes,
- difficulty in urination due to prostate enlargement,
- glaucoma,
- high blood pressure,
- mild to moderate kidney disease,
- mild to moderate liver disease,
- any other serious disease, are under doctor's care for any serious condition, or are taking any other drug including over the counter drugs,
- each 200 mg caplet contains 22 mg of sodium. This should be taken into consideration in a sodium restricted diet.

Long-term continuous use may increase the risk of heart attack or stroke.

INTERACTIONS WITH THIS MEDICATION

Do not use this product if you are taking:

- Daily low dose ASA (81 – 325 mg), without talking to a doctor or pharmacist. Ibuprofen may interfere with the preventative benefits of ASA.
- ASA or other anti-inflammatory medication.

Drugs that may interact with Advil® Headache Caplets include:

- Acetaminophen
- Acetylsalicylic acid (ASA)
- Anticoagulants (blood thinning medications)
- Anti-hypertensives (blood pressure medications)
- Benzodiazepines
- Corticosteroids
- Cyclosporine
- Diabetes medication (including insulin and oral antidiabetic agents)
- Digoxin
- Diuretics (water pills)
- Drugs for depression
- Lithium
- Methotrexate
- Nonsteroidal anti-inflammatory drugs (NSAIDs); including naproxen and ibuprofen
- Phenytoin
- Protein-bound drugs (including probenecid)
- Thyroxine

Tell your doctor or pharmacist what prescription or non-prescription drugs you are taking or plan to take.

Do not smoke or drink alcohol while using this product.

PROPER USE OF THIS MEDICATION

Usual dose:
Adults and Children 12 years and over: Take 1 caplet every 4 hours or 2 caplets every 6 to 8 hours as needed. Do not exceed 6 caplets in 24 hours, unless directed by a physician.

Do not use longer than 5 days for pain relief.
Do not use for longer than 3 days for fever.

Overdose:

In case of overdose, call a Poison Control Centre or a doctor immediately, even if there are no symptoms.

Missed Dose:
Take the missed dose as soon as you remember. If it is almost time for your next dose, wait until then to take your medicine and skip the missed dose. Do not take twice the recommended dose following a missed dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Advil® Headache Caplets may occasionally produce unwanted side effects, such as heartburn, constipation, nausea, bloating, nervousness or sleeplessness.

Stop use and contact a doctor or pharmacist if these symptoms worsen or persist.
The risk of having side effects may be decreased by using the smallest dose for the shortest duration of time.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Seek immediate emergency medical assistance
		Only if severe	In all cases	
Uncommon	Symptoms of allergic reaction, including: rash, severe itching/ redness, blisters, swelling, or trouble breathing			✓
	Blood in vomit, bloody or black stools			✓
	Abdominal pain, vomiting, diarrhea		✓	
	Ringing or buzzing in the ears / dizziness		✓	
	Change in vision,		✓	
	Fluid retention		✓	

This is not a complete list of side effect. For any unexpected effects while taking Advil® Headache Caplets, contact your doctor or pharmacist.

HOW TO STORE IT

Store at room temperature (15°-30°C).

Keep out of reach of children. This package contains enough medicine to seriously harm a child.

REPORTING SIDE EFFECTS

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting the sponsor, Pfizer Consumer Healthcare, a division of Pfizer Canada Inc., Mississauga, ON L5R 4B2, at: 1-888-275-9938 or www.advil.ca.

This leaflet was prepared by Pfizer Consumer Healthcare, a division of Pfizer Canada Inc.

Product monograph available to physicians and pharmacists upon request.

Last revised: 11-August-2017

PART III: CONSUMER INFORMATION

Advil® Headache Tablets (200 mg ibuprofen tablets, provided as 256 mg ibuprofen sodium dihydrate)

This leaflet is part III of a three-part "Product Monograph" published when Advil® Headache Tablets was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Advil® Headache Tablets. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
Fast and effective relief of headache including tension headache, toothache, menstrual pain, minor aches and pain associated with muscles, bones and joints, sprains and strains, backache, body pain, pain from inflammation associated with arthritis or physical overexertion,, and aches and pains due to the common cold and flu, in addition to reducing fevers.

Advil® Headache Tablets also provide temporary relief of mild to moderate migraine headaches including associated symptoms of nausea, and sensitivity to light and sound.

Provides up to 8 hours of long lasting pain relief.

What it does:
Ibuprofen sodium reduces pain and fever.

When it should not be used:
Do not use Advil® Headache Tablets if you have or are:
- allergic/hypersensitive to acetylsalicylic acid (ASA), ibuprofen, other salicylates, other non-steroidal anti-inflammatory drugs (NSAIDs) or any of Advil® Headache Tablet's ingredients (Refer to the nonmedicinal ingredients section of this insert),
- peptic ulcer disease, gastrointestinal bleeding or active inflammatory bowel disease (e.g. Crohn's, colitis) ,
- taking ASA or other NSAIDs including any other ibuprofen product,
- nasal polyps (swelling of the inside of the nose),
- asthma,
- allergic manifestations such as anaphylaxis (sudden severe life threatening allergic reaction), urticaria/hives, rhinitis (stuffed or runny nose that may be due to allergies), skin rash or other allergic symptoms,
- dehydrated (significant fluid loss) due to vomiting, diarrhea or lack of fluid intake,
- been diagnosed with severe high blood pressure or have heart disease,
- about to have or just had heart surgery,
- serious liver disease,
- severe kidney disease,
- thyroid disease,
- Raynaud's Syndrome (a disorder of the circulatory system),
- Systemic Lupus Erythematosus,
- pregnant or nursing.

What the medicinal ingredient is:
Ibuprofen sodium dihydrate.

What the important nonmedicinal ingredients are:
acesulfame potassium, black iron oxide, caramel colour, carnauba wax, colloidal silicon dioxide, copovidone, hypromellose, mannitol, medium chain triglycerides, microcrystalline cellulose, natural and artificial flavours, polyethylene glycol, propylene glycol, red iron oxide, sodium lauryl sulfate, sucralose, titanium dioxide, yellow iron oxide.

What dosage forms it comes in:
Advil® Headache Tablets contain ibuprofen 200 mg, provided as 256 mg ibuprofen sodium dihydrate.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- **Caution in patients with heart failure, high blood pressure or other conditions predisposing to fluid retention.**
- **Caution in patients at risk of gastrointestinal tract irritation.**
- **Caution in those at risk of kidney or liver problems, those taking diuretics and the elderly.**
- **Stop use immediately if you have difficulty or pain when urinating.**

BEFORE you use Advil® Headache Tablets talk to your doctor or pharmacist if you have:
- blood clotting disorder (such as hemophilia),
- breathing problems or chronic lung disease (such as chronic bronchitis),
- diabetes,
- difficulty in urination due to prostate enlargement,
- glaucoma,
- high blood pressure,
- mild to moderate kidney disease,
- mild to moderate liver disease,
- any other serious disease, are under doctor's care for any serious condition, or are taking any other drug including over the counter drugs,
- each 200 mg tablet contains 22 mg of sodium. This should be taken into consideration in a sodium restricted diet.

Long-term continuous use may increase the risk of heart attack or stroke.

INTERACTIONS WITH THIS MEDICATION

Do not use this product if you are taking:

- Daily low dose ASA (81 – 325 mg), without talking to a doctor or pharmacist. Ibuprofen may interfere with the preventative benefits of ASA.
- ASA or other anti-inflammatory medication.

Drugs that may interact with Advil® Headache Tablets include:

- Acetaminophen
- Acetylsalicylic acid (ASA)
- Anticoagulants (blood thinning medications)
- Anti-hypertensives (blood pressure medications)
- Benzodiazepines
- Corticosteroids
- Cyclosporine
- Diabetes medication (including insulin and oral antidiabetic agents)
- Digoxin
- Diuretics (water pills)
- Drugs for depression
- Lithium
- Methotrexate
- Nonsteroidal anti-inflammatory drugs (NSAIDs); including naproxen and ibuprofen
- Phenytoin
- Protein-bound drugs (including probenecid)
- Thyroxine

Tell your doctor or pharmacist what prescription or non-prescription drugs you are taking or plan to take.

Do not smoke or drink alcohol while using this product.

PROPER USE OF THIS MEDICATION

Usual dose:
Adults and Children 12 years and over: Take 1 tablet every 4 hours or 2 tablets every 6 to 8 hours as needed. Do not exceed 6 tablets in 24 hours, unless directed by a physician.

Do not use longer than 5 days for pain relief.
Do not use for longer than 3 days for fever.

Overdose:

In case of overdose, call a Poison Control Centre or a doctor immediately, even if there are no symptoms.

Missed Dose:
Take the missed dose as soon as you remember. If it is almost time for your next dose, wait until then to take your medicine and skip the missed dose. Do not take twice the recommended dose following a missed dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Advil® Headache Tablets may occasionally produce unwanted side effects, such as heartburn, constipation, nausea, bloating, nervousness or sleeplessness.

Stop use and contact a doctor or pharmacist if these symptoms worsen or persist.
The risk of having side effects may be decreased by using the smallest dose for the shortest duration of time.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Seek immediate emergency medical assistance
		Only if severe	In all cases	
Uncommon	Symptoms of allergic reaction, including: rash, severe itching/ redness, blisters, swelling, or trouble breathing			✓
	Blood in vomit, bloody or black stools			✓
	Abdominal pain, vomiting, diarrhea		✓	
	Ringing or buzzing in the ears / dizziness		✓	
	Change in vision,		✓	
	Fluid retention		✓	

This is not a complete list of side effect. For any unexpected effects while taking Advil® Headache Tablets, contact your doctor or pharmacist.

HOW TO STORE IT

Store at room temperature (15°-30°C).

Keep out of reach of children. This package contains enough medicine to seriously harm a child.

REPORTING SIDE EFFECTS

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting the sponsor, Pfizer Consumer Healthcare, a division of Pfizer Canada Inc., Mississauga, ON L5R 4B2, at: 1-888-275-9938 or www.advil.ca.

This leaflet was prepared by Pfizer Consumer Healthcare, a division of Pfizer Canada Inc.

Product monograph available to physicians and pharmacists upon request.

Last revised: 11-August-2017

PART III: CONSUMER INFORMATION

Advil® Headache Extra Strength (400 mg ibuprofen caplets, provided as 512 mg ibuprofen sodium dihydrate)

This leaflet is part III of a three-part "Product Monograph" published when Advil® Headache Extra Strength was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Advil® Headache Extra Strength. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
Fast and effective relief of headache including tension headache, toothache, menstrual pain, minor aches and pain associated with muscles, bones and joints, sprains and strains, backache, body pain, pain from inflammation associated with arthritis or physical overexertion, and aches and pains due to the common cold and flu, in addition to reducing fevers.

Advil® Headache Extra Strength also provides temporary relief of mild to moderate migraine headaches including associated symptoms of nausea, and sensitivity to light and sound.

Provides up to 8 hours of long lasting pain relief.

What it does:
Ibuprofen sodium reduces pain and fever.

When it should not be used:
Do not use Advil® Headache Extra Strength if you have or are:

- allergic/hypersensitive to acetylsalicylic acid (ASA), ibuprofen, other salicylates, other non-steroidal anti-inflammatory drugs (NSAIDs) or any of Advil® Headache Extra Strength's ingredients (Refer to the nonmedicinal ingredients section of this insert),
- peptic ulcer disease, gastrointestinal bleeding or active inflammatory bowel disease (e.g. Crohn's or colitis),
- taking ASA or other NSAIDs including any other ibuprofen product,
- nasal polyps (swelling of the inside of the nose),
- asthma,
- allergic manifestations such as anaphylaxis (sudden severe life threatening allergic reaction), urticaria/hives, rhinitis (stuffed or runny nose that may be due to allergies), skin rash or other allergic symptoms,
- dehydrated (significant fluid loss) due to vomiting, diarrhea or lack of fluid intake,
- been diagnosed with severe high blood pressure or have heart disease,
- about to have or just had heart surgery,
- serious liver disease,
- severe kidney disease,
- thyroid disease,
- Raynaud's Syndrome (a disorder of the circulatory system),
- Systemic Lupus Erythematosus,
- pregnant or nursing.

What the medicinal ingredient is:
Ibuprofen sodium dihydrate.

What the important nonmedicinal ingredients are:
acesulfame potassium, black iron oxide, caramel colour, carnauba wax, colloidal silicon dioxide, copovidone, hypromellose, mannitol, medium chain triglycerides, microcrystalline cellulose, natural and artificial flavours, polyethylene glycol, propylene glycol, red iron oxide, sodium lauryl sulfate, sucralose, titanium dioxide, yellow iron oxide.

What dosage forms it comes in:
Advil® Headache Extra Strength contains ibuprofen 400 mg, provided as 512 mg ibuprofen sodium dihydrate.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- **Caution in patients with heart failure, high blood pressure or other conditions predisposing to fluid retention.**
- **Caution in patients at risk of gastrointestinal tract irritation.**
- **Caution in those at risk of kidney or liver problems, those taking diuretics and the elderly.**
- **Stop use immediately if you have difficulty or pain when urinating.**

BEFORE you use Advil® Headache Extra Strength talk to your doctor or pharmacist if you have:

- blood clotting disorder (such as hemophilia),
- breathing problems or chronic lung disease (such as chronic bronchitis),
- diabetes,
- difficulty in urination due to prostate enlargement,
- glaucoma,
- high blood pressure,
- mild to moderate kidney disease,
- mild to moderate liver disease,
- any other serious disease, are under doctor's care for any serious condition, or are taking any other drug including over the counter drugs,
- each 400 mg caplet contains 44 mg of sodium. This should be taken into consideration in a sodium restricted diet.

Long-term continuous use may increase the risk of heart attack or stroke.

INTERACTIONS WITH THIS MEDICATION

Do not use this product if you are taking:

- Daily low dose ASA (81 – 325 mg), without talking to a doctor or pharmacist. Ibuprofen may interfere with the preventative benefits of ASA.

- ASA or other anti-inflammatory medication.

Drugs that may interact with Advil® Headache Extra Strength caplets include:

- Acetaminophen
- Acetylsalicylic acid (ASA)
- Anticoagulants (blood thinning medications)
- Anti-hypertensives (blood pressure medications)
- Benzodiazepines
- Corticosteroids
- Cyclosporine
- Diabetes medication (including insulin and oral antidiabetic agents)
- Digoxin
- Diuretics (water pills)
- Drugs for depression
- Lithium
- Methotrexate
- Nonsteroidal anti-inflammatory drugs (NSAIDs), including naproxen and ibuprofen
- Phenytoin
- Protein-bound drugs (including probenecid)
- Thyroxine

Tell your doctor or pharmacist what prescription or non-prescription drugs you are taking or plan to take.

Do not smoke or drink alcohol while using this product.

PROPER USE OF THIS MEDICATION

Usual dose:
Adults and Children 12 years and over: Take 1 caplet every 6 to 8 hours as needed. Do not exceed 3 caplets in 24 hours, unless directed by a physician.

Do not use longer than 5 days for pain relief.
Do not use for longer than 3 days for fever.

Overdose:

In case of overdose, call a Poison Control Centre or a doctor immediately, even if there are no symptoms.

Missed Dose:
Take the missed dose as soon as you remember. If it is almost time for your next dose, wait until then to take your medicine and skip the missed dose. Do not take twice the recommended dose following a missed dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Advil® Headache Extra Strength may occasionally produce unwanted side effects, such as heartburn, constipation, nausea, bloating, nervousness or sleeplessness.

Stop use and contact a doctor or pharmacist if these symptoms worsen or persist.

The risk of having side effects may be decreased by using the smallest dose for the shortest duration of time.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Seek immediate emergency medical assistance
		Only if severe	In all cases	
Uncommon	Symptoms of allergic reaction, including: rash, severe itching/ redness, blisters, swelling, or trouble breathing			✓
	Blood in vomit, bloody or black stools			✓
	Abdominal pain, vomiting, diarrhea		✓	
	Ringing or buzzing in the ears / dizziness		✓	
	Change in vision,		✓	
	Fluid retention		✓	

This is not a complete list of side effects. For any unexpected effects while taking Advil® Headache Extra Strength, contact your doctor or pharmacist.

HOW TO STORE IT

Store at room temperature (15°-30°C).

Keep out of reach of children. This package contains enough medicine to seriously harm a child.

REPORTING SIDE EFFECTS

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

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This leaflet was prepared by Pfizer Consumer Healthcare, a division of Pfizer Canada Inc.

Product monograph available to physicians and pharmacists upon request.

Last revised: 11-August-2017