SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Advil Children's Grape Flavor
Advil Children's Fruit Flavor

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Ibuprofen 100mg/5ml.

Excipients with known effect:
Sucrose
Sodium
Sorbitol
Sodium Benzoate
Propylene Glycol (Grape Flavor only)
Benzyl Alcohol (Fruit Flavor only)

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Suspension.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the reduction of fever and relief of mild to moderate pain.
For infants and children aged 3 months to 12 years.

4.2 Posology and method of administration

Posology
The lowest effective dose should be used for the shortest duration necessary to relieve symptoms (see section 4.4).

For pain and fever: The daily dosage of Children's Advil aged 6 months to 12 years old is 5 to 10 mg/kg ORALLY every 6 to 8 hours as needed MAX 4 doses/day.
Infants and children aged 3 -6 months: dosage according to physician’s prescription only. Children with identical ages can have significantly different weights. Therefore, try to obtain the weight of the child and determine the dosage by weight. Only if you cannot find the child's weight determine the dosage according to age.

Using the measuring cup or syringe dosing device provided this can be achieved as follows:

Dosing chart

Weight	**Age**	**Dosage**	**Number of times in 24 hours**
Under 5 kg	3 – 6 months	According to physician's prescription only	
5 – 5.4 kg		2 ml	3 – 4 times
5.5 – 8.1 kg	6 – 11 months	2.5 ml	
8.2 – 10.9 kg	12 – 23 months	3.75 ml	
11 – 15 kg	2 – 3 years	5 ml	
16 – 21 kg	4 – 5 years	7.5 ml	
22 – 26 kg	6 – 8 years	10 ml	
27 – 32 kg	9 – 10 years	12.5 ml	
33 – 43 kg	11 – 12 years	15 ml	

Doses should be given approximately every 6 to 8 hours, (or with a minimum of 4 hours between each dose if required).
For short term use only.
If the child's (aged over 6 months) symptoms persist for more than 3 days, consult your doctor.
For children aged 3-6 months, medical advice should be sought after 24 hours use (3 doses) if symptoms persist.
The lowest effective dose should be used for the shortest duration necessary to relieve symptoms (see section 4.4).

Method of administration
For oral administration.

For patients with sensitive stomachs the product can be taken with or after food.

4.3 Contraindications
Hypersensitivity to ibuprofen or to any of the excipients listed in section 6.1.

Patients who have previously shown hypersensitivity reactions (e.g. asthma, rhinitis, angioedema or urticaria) in response to ibuprofen, acetylsalicylic acid (aspirin) or other non-steroidal anti-inflammatory drugs (NSAIDs).

Active or a history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding).

History of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy.

Severe hepatic failure, renal failure or heart failure (See section 4.4, Special warnings and precautions for use).

Last trimester of pregnancy (See section 4.6 Pregnancy and lactation).

4.4 Special warnings and precautions for use
Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see GI and cardiovascular risks below).

The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal.

Respiratory:
Bronchospasm may be precipitated in patients suffering from or with a previous history of bronchial asthma or allergic disease.

Other NSAIDs:
The use of Ibuprofen with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided (see section 4.5).

SLE and mixed connective tissue disease:
Systemic lupus erythematosus and mixed connective tissue disease, due to increased risk of aseptic meningitis (see section 4.8).

Cardiovascular and cerebrovascular effects:
Caution (discussion with doctor or pharmacist) is required prior to starting treatment in patients with a history of hypertension and/or heart failure as fluid retention, hypertension and oedema have been reported in association with NSAID therapy.

Clinical trial and epidemiological data suggest that use of ibuprofen, particularly at high doses (2400mg daily) and in long-term treatment may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke). Overall, epidemiological studies do not suggest that low dose ibuprofen (e.g. ≤ 1200mg daily) is associated with an increased risk of myocardial infarction.

Renal:
Renal impairment as renal function may further deteriorate (See section 4.3 and Section 4.8).
There is a risk of renal impairment in dehydrated children (See section 4.3 and section 4.8).

Hepatic:
Hepatic dysfunction (See section 4.3 and 4.8).

Impaired female fertility:
There is limited evidence that drugs which inhibit cyclo-oxygenase/ prostaglandin synthesis may cause impairment of female fertility by an effect on ovulation. This is reversible upon withdrawal of treatment.

Gastrointestinal effects:
NSAIDs should be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) as their conditions may be exacerbated (see section 4.8).

Gastrointestinal bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at anytime during treatment, with or without warning symptoms or a previous history of serious GI events.

The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (see section 4.3), and in the elderly. These patients should commence treatment on the lowest dose available.

Patients with a history of GI toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially GI bleeding) particularly in the initial stages of treatment.

Caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors or anti-platelet agents such as acetylsalicylic acid (aspirin) (see section 4.5).

When GI bleeding or ulceration occurs in patients receiving ibuprofen, the treatment should be withdrawn.

Severe skin reactions:
Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs (see section 4.8). Patients appear to be at highest risk for these reactions early in the course of therapy: the onset of the reaction occurring in the majority of cases within the first month of treatment. Acute generalized exanthematous pustulosis (AGEP) has been reported in relation to ibuprofen-containing products.

Ibuprofen should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Masking of symptoms of underlying infections:
Children's Advil can mask symptoms of infection, which may lead to delayed initiation of appropriate treatment and thereby worsening the outcome of the infection. This has been observed in bacterial community acquired pneumonia and bacterial complications to varicella. When Children's Advil is administered for fever or pain relief in relation to infection, monitoring of infection is advised. In non-hospital settings, the patient should consult a doctor if symptoms persist or worsen.

Exceptionally, varicella can be at the origin of serious cutaneous and soft tissues infectious complications. Thus, it is advisable to avoid use of Children’s Advil in case of varicella.

This medicine contains sucrose at a concentration of 2.5 g / 5 ml. This should be taken into account in patients with diabetes mellitus .
This medicine contains less than 1 mmol sodium (23 mg) per 15 ml, that is to say essentially ‘sodium-free’.

This medicine contains sorbitol. Sorbitol may cause gastrointestinal discomfort and mild laxative effect.
This medicine contains 12.5 mg Sodium benzoate in each 5 ml.
Advil Children's Fruit Flavor contains a maximum of 0.4mg benzyl alcohol in each mL of suspension. Benzyl alcohol may cause allergic reactions.
Advil Children's Grape Flavor contains 1.9mg of propylene glycol in each mL of suspension.

4.5 Interaction with other medicinal products and other forms of interaction

Ibuprofen should be avoided in combination with:

- *Acetylsalicylic acid (aspirin):* Unless low-dose acetylsalicylic acid (aspirin) (not above 75mg daily) has been advised by a doctor, as this may increase the risk of adverse reactions (See section 4.4).

  Experimental data suggest that ibuprofen may inhibit the effect of low dose acetylsalicylic acid (aspirin) on platelet aggregation when they are dosed concomitantly. However, the limitations of these data and the uncertainties regarding extrapolation of ex vivo data to the clinical situation imply that no firm conclusions can be made for regular ibuprofen use, and no clinically relevant effect is considered to be likely for occasional ibuprofen use (see section 5.1).

- *Other NSAIDs including cyclooxygenase-2 selective inhibitors*: Avoid concomitant use of two or more NSAIDs as this may increase the risk of adverse effects (see section 4.4)

Ibuprofen should be used with caution in combination with:
Anticoagulants: NSAIDS may enhance the effects of anti-coagulants, such as warfarin (See section 4.4).

Antihypertensives (ACE inhibitors and Angiotensin II antagonists) and diuretics: NSAIDs may diminish the effect of these drugs. Diuretics can increase the risk of nephrotoxicity of NSAIDs.

Corticosteroids: Increased the risk of gastrointestinal ulceration or bleeding (see Section 4.4)

Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs): increased risk of gastrointestinal bleeding (see section 4.4).

Cardiac glycosides: NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma glycoside levels.

Lithium: There is evidence for potential increases in plasma levels of lithium.

Methotrexate: There is a potential for an increase in plasma levels of methotrexate.

Ciclosporin: Increased risk of nephrotoxicity.

Mifepristone: NSAIDs should not be used for 8-12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone.

Tacrolimus: Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus

Zidovudine: Increased risk of haematological toxicity when NSAIDs are given with zidovudine. There is evidence of an increased risk haemarthroses and haematoma in HIV (positive) haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.

Quinolone antibiotics: Animal data indicate that NSAIDs can increase the risk of convulsions associated with quinolone antibiotics. Patients taking NSAIDs and quinolones may have an increased risk of developing convulsions

4.6 Fertility, pregnancy and lactation

Pregnancy
Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1%, up to approximately 1.5 %. The risk is believed to increase with dose and duration of therapy. In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-foetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period.

During the first and second trimester of pregnancy, Children's Advil should not be given unless clearly necessary. If Children's Advil is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible.

Rarely, taking NSAIDs after the 20th week of pregnancy may cause impaired renal function of the fetus, which may cause low levels of amniotic fluid (oligohydramnios).

These effects were observed after days to weeks of treatment. However, in rare cases, low levels of amniotic fluid were observed already after 48 hours of taking NSAIDs. In most cases, oligohydramnios passed with the treatment discontinuation.

Using NSAIDs after the 20th week of pregnancy should be limited. If it was decided that the benefit outweighs the risk for the fetus, the lowest effective dose should be used for the shortest possible period.

Referring the patient to ultrasound scan should be considered, in order to estimate the amount of amniotic fluid when the treatment with the therapeutic dosage of these

medicines exceeding 5 days and stopping the treatment if low levels of amniotic fluid is detected.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to:

- cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension);
- renal dysfunction, which may progress to renal failure with oligo-hydroamniosis; the mother and the neonate, at the end of pregnancy, to:
- possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses.
- inhibition of uterine contractions resulting in delayed or prolonged labour.

Consequently, Children's Advil is contraindicated during the third trimester of pregnancy.

Breast-feeding
In limited studies, ibuprofen appears in the breast milk in very low concentration and is unlikely to affect the breast fed infant adversely.

Fertility
See section 4.4 regarding female fertility.

4.7 Effects on ability to drive and use machines
None expected at recommended doses and duration of therapy.

4.8 Undesirable effects
The following list of adverse effects relates to those experienced with ibuprofen at OTC doses (maximum 1200 mg ibuprofen per day), in short-term use. In the treatment of chronic conditions, under long-term treatment, additional adverse events may occur.

Adverse events which have been associated with ibuprofen are given below, tabulated by system organ class and frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 and <1/10), uncommon (≥1/1000 and <1/100), rare (≥1/10,000 and <1/1000), very rare (< 1/10,000) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse events are presented in order of decreasing seriousness. The most commonly observed adverse events are gastrointestinal in nature.

System Organ Class	Frequency	Adverse Events
Blood and Lymphatic System Disorders	Very rare	Haematopoietic disorders, anaemia, leucopenia, thrombocytopenia, pancytopenia and agranulocytosis[1]
Immune System Disorders	Uncommon	Hypersensitivity with urticaria and pruritus[2]
	Very rare	Severe hypersensitivity reactions, including facial, tongue and throat swelling, dyspnoea, tachycardia, and hypotension (anaphylaxis, angioedema or severe shock)[2]
Nervous System Disorders	Uncommon	Headache
	Very rare	Aseptic meningitis[3]

Cardiac Disorders	Not known	Cardiac failure and Oedema[4]
Vascular Disorders	Not known	Hypertension[4]
Respiratory, Thoracic and Mediastinal Disorders	Not known	Respiratory tract reactivity comprising asthma, bronchospasm or dyspnoea[2]
Gastrointestinal Disorders	Uncommon	Abdominal pain, nausea and dyspepsia[5]
	Rare	Diarrhoea, flatulence, constipation and vomiting
	Very rare	Peptic ulcer, gastrointestinal perforation or Gastrointestinal haemorrhage, melaena, and haematemesis[6]. Mouth ulceration and gastritis. Exacerbation of colitis and Crohn's disease[7]
Hepatobiliary Disorders	Very rare	Liver disorder
Skin and Subcutaneous Tissue Disorders	Uncommon	Skin rash[2]
	Very rare	Bullous reactions, including Stevens-Johnson Syndrome, erythema multiforme and toxic epidermal necrolysis[2]
	Not known	Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome) Acute generalized exanthematous pustulosis (AGEP) Photosensitivity reactions
Renal and Urinary Disorders	Very rare	Acute renal failure, papillary necrosis, especially in long-term use, associated with Increased serum urea and oedema[8]
Investigations	Very rare	Haemoglobin decreased
Infections and infestations	Not known	Exacerbation of infections related inflammation has been described, in exceptional cases, severe skin infections and soft tissue complications may occur during a varicella infection.

Description of Selected Adverse Reactions

[1] First signs are fever, sore throat, superficial mouth ulcers, flu-like symptoms, severe exhaustion, unexplained bleeding and bruising.

[2] Hypersensitivity reactions: These may consist of (a) non-specific allergic reactions and anaphylaxis, (b) respiratory tract reactivity, including asthma, aggravated asthma, bronchospasm, and dyspnoea, or (c) various skin reactions, including pruritus, urticaria, purpura, angioedema and, more rarely, exfoliative and bullous dermatoses, including toxic epidermal necrolysis, Stevens-Johnson Syndrome and erythema multiforme.

[3] The pathogenic mechanism of drug-Induced aseptic meningitis is not fully understood. However, the available data on NSAID-related aseptic meningitis points to a hypersensitivity reaction (due to a temporal relationship with drug intake, and disappearance of symptoms after drug discontinuation). Of note, single cases of symptoms of aseptic meningitis (such as stiff neck, headache, nausea, vomiting, fever or disorientation) have been observed during treatment with ibuprofen in patients with existing auto-immune disorders (such as systemic lupus erythematosus and mixed connective tissue disease).

[4] Clinical trial and epidemiological data suggest that use of ibuprofen (particularly at high doses 2400 mg daily) and in long-term treatment may be associated with a small increased risk of arterial thrombotic events (e.g. myocardial infarction or stroke), (see section 4.4).

[5] The adverse events observed most often are gastrointestinal in nature.

[6] Sometimes fatal.

[7] See section 4.4.

[8] Especially in long-term use, associated with increased serum urea and oedema. Also includes papillary necrosis.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/

4.9 Overdose

In children ingestion of more than 400 mg/kg may cause symptoms. In adults the dose response effect is less clear cut. The half-life in overdose is 1.5-3 hours.

Symptoms

Most patients who have ingested clinically important amounts of NSAIDs will develop no more than nausea, vomiting, epigastric pain, or more rarely diarrhoea. Tinnitus, headache and gastrointestinal bleeding are also possible. In more serious poisoning, toxicity is seen in the central nervous system, manifesting as drowsiness, occasionally excitation and disorientation or coma. Occasionally patients develop convulsions. In serious poisoning metabolic acidosis may occur and the prothrombin time/ INR may be prolonged, probably due to interference with the actions of circulating clotting factors. Acute renal failure and liver damage may occur. Exacerbation of asthma is possible in asthmatics.

Management

Management should be symptomatic and supportive and include the maintenance of a clear airway and monitoring of cardiac and vital signs until stable. Consider oral administration of activated charcoal if the patient presents within 1 hour of ingestion of a potentially toxic amount. If frequent or prolonged, convulsions should be treated with intravenous diazepam or lorazepam. Give bronchodilators for asthma.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Anti-inflammatory and anti-rheumatic products, non-steroids, propionic acid derivative; **ATC Code:** M01AE01

Ibuprofen is a propionic acid derivative NSAID that has demonstrated its efficacy by inhibition of prostaglandin synthesis. In humans ibuprofen reduces inflammatory pain, swellings and fever. Furthermore, ibuprofen reversibly inhibits platelet aggregation.

Experimental data suggest that ibuprofen may inhibit the effect of low dose aspirin on platelet aggregation when they are dosed concomitantly. In one study, when a single dose of ibuprofen 400mg was taken within 8 h before or within 30 min after

immediate release aspirin dosing (81mg), a decreased effect of ASA on the formation of thromboxane or platelet aggregation occurred. However, the limitations of these data and the uncertainties regarding extrapolation of ex vivo data to the clinical situation imply that no firm conclusions can be made for regular ibuprofen use, and no clinically relevant effect is considered to be likely for occasional use.

Clinical evidence demonstrates that:

- 5 mg/kg of ibuprofen can provide up to 6 hour fever relieving effect
- 6 mg/kg of ibuprofen and above can provide up to 8 hour fever relieving effect
- 5 mg/kg of ibuprofen and above can provide up to 8 hour pain relieving effect

5.2 Pharmacokinetic properties
Ibuprofen is rapidly absorbed following administration and is rapidly distributed throughout the whole body. The excretion is rapid and complete via the kidneys. Maximum plasma concentrations are reached 45 minutes after ingestion if taken on an empty stomach. When taken with food, peak levels are observed after 1 to 2 hours. These times may vary with different dosage forms.

The half-life of ibuprofen is about 2 hours.

In limited studies, ibuprofen appears in the breast milk in very low concentrations.

5.3 Preclinical safety data
There are no preclinical safety data of relevance to the consumer.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Grape Flavored Suspension – Inactive Ingredients:
Sucrose, Sorbitol Solution, Glycerin, Microcrystalline cellulose, Polysorbate 80 , Sodium Benzoate, Citric Acid Hydrous, Grape Flavor Art. # 6175, Xantan Gum, Carboxymethylcellulose Sodium, Disodium Edetate, FD&C Red # 40, FD&C Blue # 1, Purified Water.

Fruit Flavored Suspension – Inactive Ingredients:
Sucrose, Sorbitol Solution, Glycerin, Microcrystalline cellulose, Polysorbate 80, Sodium Benzoate, Citric Acid Hydrous, Xantan Gum, Carboxymethylcellulose Sodium, Tutti Frutti Art. Flavor 51880A , Disodium Edetate, FD&C Red # 40, Purified Water.

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
The expiry date of the product is indicated on the packaging materials

6.4 Special precautions for storage
Store below 25°C.

The expiry date after first opening is identical to the expiry date printed on the package.

6.5 Nature and contents of container
Grape Flavored Suspension: a translucent, purple liquid packed in a 120 ml plastic bottle with child resistant cap .
Fruit Flavored Suspension: a translucent, red suspension packed in a 60 ml or 120 ml plastic bottle with child resistant cap.

6.6 Special precautions for disposal
Not applicable

7 MANUFACTURER

Fareva Richmond Inc. Virginia, USA

8 REGISTRATION HOLDER

GSK Consumer Healthcare Israel Ltd., 25 Basel St., P.O.B 3256, Petach Tikvah

9 REGISTRATION NUMBER OF THE MEDICINE IN THE NATIONAL DRUG REGISTRY OF THE MINISTRY OF HEALTH

Advil Children's Grape Flavor	122-43-30111
Advil Children's Fruit Flavor	122-42-30110

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