## 1. NAME OF THE MEDICINAL PRODUCT
# Advil Forte 400

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each capsule contains Ibuprofen 400mg
Contains sorbitol (E420), lecithin.
For a full list of excipients, see section 6.1

## 3. PHARMACEUTICAL FORM
Oval capsule with a dye free, translucent gelatine shell, printed with '400' in black ink, and contains a clear liquid fill.

## 4. CLINICAL PARTICULARS
### 4.1 Therapeutic indications
Relief of mild to moderate pain such as headache, pain associated with migraine, toothache, menstrual pain, backache, muscular pain, anti-inflammatory for rheumatic disease, reduction of fever.

### 4.2 Posology and method of administration
For oral administration and short-term use only.
The lowest effective dose should be used for the shortest duration necessary to relieve symptoms (see section 4.4).

For all indications:
Adults, older people and children and adolescents between 12-18 years of age:
If in children or adolescents between 12 -18 years of age, this medicinal product is required for more than 3 days, or if symptoms worsen, a doctor should be consulted.

For adults aged 18 years or older, the lowest effective dose should be used for the shortest duration necessary to relieve symptoms and minimise undesirable effects (see section 4.4). The patient should consult a doctor if symptoms persist or worsen, or if the product is required for more than 10 days.

One capsule up to three times per day as required. The respective dosing interval should be chosen in line with the observed symptoms and the maximum recommended daily dose. Doses should be given approximately every 6-8 hours, with a minimum interval of 4 hours between each dose. A total dose of 1200 mg of ibuprofen (3 capsules) should not be exceeded in any 24 hour period. The capsules should be taken with water.

Not to be used for children under 12 years of age.

### 4.3 Contraindications
Hypersensitivity to ibuprofen or any of the other ingredients in the product (see Section 4.4 Special Warnings and Precautions and Section 6.1 List of excipients).

Use in patients hypersensitive to aspirin or with bronchospasm, asthma, rhinitis, angioedema or urticaria associated with non-steroidal anti-inflammatory drugs (NSAIDs).

Ibuprofen should not be given to patients with active or 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 NSAID therapy.

Cerebrovascular bleeding, other active bleeding, or haematological disease.

Severe hepatic failure, severe renal failure or severe heart failure (NYHA Class IV).

Last trimester of pregnancy (see section 4.6 Fertility, 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 gastrointestinal and cardiovascular risks below).

*Older people:*
Older people 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 and Advil Forte 400 should not be used where other NSAIDs have produced reactions.

*Other NSAIDs:*
The use of Advil Forte 400 with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided (See section 4.5).

*Systemic Lupus Erythematosus (SLE) and mixed connective tissue disease:*
Caution should be taken when ibuprofen is given to patients with SLE and autoimmune diseases – increased risk of aseptic meningitis has been reported (see section 4.8).

*Renal, Cardiac and Hepatic:*
Caution is required in patients with renal, cardiac or hepatic impairment since renal function may deteriorate (see sections 4.3 and 4.8). The dose should be as low as possible and renal function should be monitored.

There is a risk of renal impairment in dehydrated children or adolescents between 12 -18 years of age.

*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 studies suggest that use of ibuprofen, particularly at high doses (2400mg/day) 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. ≤ 1200 mg/day) is associated with an increased risk of arterial thrombotic events.
Patients with uncontrolled hypertension, congestive heart failure (NYHA II-III), established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with ibuprofen after careful consideration and high doses (2400 mg/day) should be avoided.

Careful consideration should also be exercised before initiating long-term treatment of patients with risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus and smoking), particularly if high doses of ibuprofen (2400 mg/day) are required.

*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:*

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

GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at any time 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 (SSRIs) or anti-platelet agents such as aspirin (see section 4.5).

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

*Dermatological:*
Severe skin reactions
Severe 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. Advil Forte 400 should be discontinued at the first appearance of skin rash, mucosal lesions or any other sign of hypersensitivity.

*Masking of symptoms of underlying infections*
Advil Forte 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 Advil Forte 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.

The pharmacological activity of Ibuprofen may reduce fever and inflammation, thus diminishing their utility as diagnostic signs in detecting underlying conditions.

Patients with rare hereditary problems of fructose intolerance should not take this medicine.

Advil Forte 400 Capsules contain soya lecithin. If you are allergic to peanut or soya, do not use this medicinal product.

**4.5 Interaction with other medicinal products and other forms of interaction**
**Ibuprofen should be avoided in combination with:**
*Aspirin:*

Concomitant administration of ibuprofen and aspirin is not generally recommended because of the potential of increased adverse effects.

Experimental data suggest that ibuprofen may competitively inhibit the effect of low dose aspirin on platelet aggregation when they are dosed concomitantly. Although there are uncertainties regarding extrapolation of these data to the clinical situation, the possibility that regular, long-term use of ibuprofen, may reduce the cardioprotective effect of low-dose aspirin cannot be excluded.
No clinically relevant effect is considered to be likely for occasional ibuprofen use (see section 5.1).

*Other NSAIDs:*
Ibuprofen should not be used with other pain relievers such as NSAIDs.

**Ibuprofen should be used with caution in combination with:**
*Anticoagulants*: NSAIDs may enhance the effects of anticoagulants such as warfarin (see section 4.4). When taking anticoagulants it should be taken into account that long-term use of ibuprofen may increase the risk of bleeding.

*Antihypertensives and diuretics*: NSAIDs may diminish the effects of antihypertensives or thiazide diuretics. Diuretics can increase the risk of nephrotoxicity of NSAIDs.

*Corticosteroids*: When taking corticosteroids and ibuprofen concomitantly there is an increased 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*: Ibuprofen may increase serum digitalis concentrations. Serum digitalis concentrations should therefore be monitored in patients with decreased renal function or congestive heart failure.

*Lithium*: Increases in serum lithium concentrations following administration of ibuprofen may be clinically significant.

*Methotrexate*: Concomitant administration of ibuprofen with moderate and high doses of methotrexate may lead to serious and fatal methotrexate toxicity. Patients with reduced renal function may be at additional risk of toxicity from the combination even when low doses of methotrexate (≤20 mg/week) are used.

*Ciclosporin*: Increased risk of nephrotoxicity.
*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 of haemarthroses and haematoma in HIV(+) 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.

*Phenytoin:* Ibuprofen may increase pharmacologically active free phenytoin. Patients taking ibuprofen for long-term use should be monitored.

*Antacids:* Certain antacids may increase the gastrointestinal absorption of ibuprofen. This is considered to be of clinical relevance particularly during long-term use of ibuprofen.

**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, ibuprofen should not be given unless clearly necessary. If ibuprofen 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.

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, ibuprofen is contraindicated during the third trimester of pregnancy.

Rarely, the use of nonsteroidal anti-inflammatory drugs (NSAIDs) after 20 weeks gestation in pregnancy may cause fetal renal dysfunction leading to oligohydramnios.

These effects are seen after days to weeks of treatment. Although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. Oligohydramnios is often, but not always, reversible with treatment discontinuation.

The use of NSAIDs after week 20 of gestation should be restricted. If the benefit of NSAID treatment is considered greater than the risk, limit use to the lowest effective dose and shortest duration possible.

Consider ultrasound monitoring of amniotic fluid if NSAID treatment of this medicine at the full treatment dosage extends beyond five days. Discontinue the NSAID if oligohydramnios occurs.

*Lactation*
In limited studies, ibuprofen appears in breast milk in very low concentrations. Based upon the low level detected (0.0008% of maternal dose), it 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**
No studies on the effect of ability to drive or use machines have been performed.
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, for short-term use. In the treatment of chronic conditions, under long-term treatment, additional adverse effects may occur.

The adverse effects have been listed in order of decreasing frequency, using the following convention: very common (≥ 1/10); common (≥ 1/100 to <1/10); uncommon (≥ 1/1,000 to <1/100); rare (≥ 1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

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| Investigations: | Very rare: | Decreased haematocrit and haemoglobin levels. |
| Cardiac Disorders: | Not known: | Oedema, hypertension, angina pectoris and cardiac failure, have been reported in association with NSAID treatment.<br><br>Clinical studies suggest that use of ibuprofen (particularly at a high dose (2400mg/day) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke) (see section 4.4). |
| Blood and Lymphatic System Disorders: | Very rare: | Haematopoietic disorders (anaemia, haemolytic anaemia, aplastic anaemia, leucopenia, thrombocytopenia, pancytopenia, agranulocytosis). First signs are: fever, sore throat, superficial mouth ulcers, influenza-like symptoms, severe exhaustion, unexplained bleeding and bruising. |
| Nervous System Disorders: | Uncommon: | Headache, dizziness, cerebrovascular accident |
| | Very rare: | Aseptic meningitis – single cases have been reported very rarely. |
| Eye Disorders: | Very rare: | Visual disturbance. |
| Ear and Labyrinth Disorders: | Very rare: | Tinnitus and vertigo. |
| Respiratory, Thoracic and Mediastinal Disorders: | Very rare: | Asthma, bronchospasm, dyspnoea and wheezing. |
| Gastrointestinal Disorders: | | The most commonly-observed adverse events are gastrointestinal in nature. |

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| | Uncommon: | Abdominal pain, abdominal distension, nausea and dyspepsia. |
| | Rare: | Diarrhoea, flatulence, constipation and vomiting. |
| | Very rare: | Peptic ulcer, perforation or gastrointestinal haemorrhage, melaena, haematemesis, sometimes fatal, particularly in the elderly, ulcerative stomatitis, gastritis, mouth ulcer. |
| | Not known: | Exacerbation of colitis and Crohn's disease (see section 4.4). |
| Renal and Urinary Disorders: | Very rare: | Acute renal failure, interstitial nephritis, nephritic syndrome, papillary necrosis, especially in long-term use, associated with increased serum urea and oedema; haematuria and proteinuria. |
| Skin and Subcutaneous Tissue Disorders: | Uncommon: | Various skin rashes |
| | Very rare: | Severe forms of skin reactions such as bullous reactions, including Stevens-Johnson Syndrome, erythema multiforme and toxic epidermal necrolysis can occur. |
| | Not known: | Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome) Acute generalised exanthematous pustulosis (AGEP) |
| Infections and Infestations: | Not known: | Meningitis, aseptic meningitis. |
| Vascular Disorders: | Very rare: | Hypertension. |
| General Disorders and Administration Site Conditions: | Very rare: | Oedema, swelling and peripheral oedema. |
| Immune System Disorders: | Uncommon: | Hypersensitivity reactions with urticaria and pruritis. |
| | Very rare: | Severe hypersensitivity reactions. Symptoms could be: facial, tongue and |

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| | | laryngeal swelling, dyspnoea, tachycardia, hypotension (anaphylaxis, angioedema or severe shock). |
| | Not known: | Non-specific allergic reactions<br>Respiratory tract reactivity (e.g. asthma, aggravated asthma and bronchospasm).<br>Various skin reactions including exfoliative and bullous dermatoses (including epidermal necrolysis and erythema multiforme).<br>In patients with existing auto-immune disorders (such as systemic lupus erythematosus, mixed connective tissue disease) during treatment with ibuprofen, single cases of symptoms of aseptic meningitis, such as stiff neck, headache, nausea, vomiting, fever or disorientation have been observed (see section 4.4). |
| Hepatobiliary Disorders: | Very rare: | Liver disorders, hepatitis and jaundice. |
| Psychiatric Disorders: | Very rare: | Nervousness. |

**Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation 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

Healthcare professionals are asked to report any suspected adverse reactions to email: il.safety@gsk.com

**4.9 Overdose**

In children ingestion of more than 400mg/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, hypotension and disorientation or coma. Occasionally patients develop convulsions. In serious poisoning and 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:** Propionic acid derivatives

**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.

Clinical evidence demonstrates that when 400 mg of ibuprofen are taken, pain relieving effects can last for up to 8 hours.

Experimental data suggest that ibuprofen may competitively inhibit the effect of low dose aspirin on platelet aggregation when they are dosed concomitantly. Some pharmacodynamic studies show that when single doses of ibuprofen 400mg were taken within 8 hours before or within 30 minutes after immediate release aspirin dosing (81mg), a decreased effect of aspirin on the formation of thromboxane or platelet aggregation occurred. Although there are uncertainties regarding extrapolation of these data to the clinical situation, (for) the possibility that regular, long-term use of ibuprofen may reduce cardioprotective effect of low-dose aspirin cannot be excluded. No clinically relevant effect is considered to be likely for occasional ibuprofen use (see section 4.5).

### 5.2 Pharmacokinetic properties

The ibuprofen from Advil Forte 400 mg capsules is absorbed to the same extent as ibuprofen from Advil tablets, the AUC(0-inf) being equivalent. After oral administration, Advil Forte 400 mg capsules show a Tmax at approximately 35 minutes (compared to Advil 400 mg tablets at approximately 90 minutes). This difference seen in Tmax has been investigated only in pharmacokinetic studies.

Ibuprofen protein binding is approximately 99%. After an oral dose, ibuprofen is 75 – 85% excreted in the urine during the first 24 hours (mainly in the form of two metabolites), the remainder being eliminated in the faeces following excretion in bile. Excretion is complete within 24 hours.

The half-life of ibuprofen in plasma is approximately 2 hours.

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

### 5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential. No teratogenic effect has been demonstrated in animal experiments, however, use of ibuprofen during pregnancy should, if possible, be avoided.

Preclinical effects were observed only at exposures considered sufficiently in excess of the maximum human exposure, indicating little relevance to clinical use.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Macrogol 600

Gelatin
Purified water
Sorbitol liquid, partially dehydrated
Potassium hydroxide 50% w/w solution
Opacode black ink (ethanol and ethyl acetate, propylene glycol (E1520), black iron oxide (E172), polyvinyl acetate phthalate, purified water, isopropyl alcohol, macrogol 400, aluminium hydroxide)
Triglycerides, medium chain
Phosal solution in ethanol
Lecithin in triglycerides (medium chain).

**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.

**6.5 Nature and contents of container**
Advil Forte 400 are packed into blister strips in a cardboard box.
Pack A: Blister: White opaque thermoformed unplasticised PVC (250 µm) / Polyethylene extrusion coating (30 µm) / PVdC (90 gsm) heat sealed to the foil.
A pack range will consist of packs of 4, 6, 8, 10, 12, 16, 20, 24, 30, 32, 36, 48, 50, 60, 96 and 100 Liquigel capsules.
Not all pack sizes may be marketed.

**6.6 Special precautions for disposal**
No special requirements

**7. MANUFACTURER**
Pfizer Consumer Manufacturing Italy S.R.L.
Via Nettunense 90,
Aprilia,
Italy

**8. REGISTRATION HOLDER**
GSK Consumer Healthcare Israel, Ltd.
P.O.B 3256, Petach Tikva, 4951038

**9. LICENSE NUMBER**
145-20-32014

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