1. **NAME OF THE MEDICINAL PRODUCT**

*Advil Forte 400*, Capsules Liquid Filled

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each capsule contains 400mg Ibuprofen
For excipients, see 6.1

3. **PHARMACEUTICAL FORM**

Soft capsule
A 14 oval capsule with a dye free, translucent gelatin shell, printed with '400' in black ink, and containing 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.
**Adults, the elderly and young persons over 12 years of age:**
The minimum effective dose should be used for the shortest time necessary to relieve symptoms. If the product is required for more than 10 days or if the symptoms worsen, the patient should consult a doctor.
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.
1 capsule up to 3 times a day, as required.
The capsules should be taken with water.
Doses should be given approximately every 6-8 hours, with a minimum interval of 4 hours between each dose. Do not take more than 1200 mg (3 capsules) in any 24 hour period.
Not to be used for children under 12 years of age.

4.3 Contraindications

- Hypersensitivity to ibuprofen or any of the constituents in the product.
- Patients who have previously shown hypersensitivity reactions (e.g. bronchospasm, asthma, rhinitis, angiodema or urticaria) in response to aspirin or other non-steroidal anti-inflammatory drugs.
- Active or previous 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. (See section 4.4).
- Use in third trimester of pregnancy (see section 4.6).

4.4 Special warnings and precautions for use

Caution is required in patients with certain conditions:
- systemic lupus erythematosus as well as those with mixed connective tissue disease due to increased risk of aseptic meningitis (see section 4.8).
- gastrointestinal disorders and chronic inflammatory intestinal disease as these conditions may be exacerbated (ulcerative colitis, Crohn's disease) (see section 4.8).
- 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.

Undesirable effects may be minimised by using the minimum effective dose for the shortest possible duration (see GI and cardiovascular risks below).

The elderly are at increased risk of the serious consequences of adverse reactions to NSAIDs, especially gastrointestinal bleeding and perforation which may be fatal.

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

Use with concomitant NSAIDs including cyclo-oxygenase-2 specific inhibitors should be avoided (See section 4.5).

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. ≤ 1200 mg daily) is associated with an increased risk of myocardial infarction.

Impaired female fertility:

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

Gastrointestinal:
GI 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 (including ulcerative colitis, Crohn's disease).

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 the 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 gastrototoxicity or bleeding, such as corticosteroids, or anticoagulants such as warfarin, selective serotonin re-uptake inhibitors (SSRIs) or anti-platelet agents such as aspirin (see section 4.5).

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

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

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 mg 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 not be used in combination with:

Aspirin: unless low dose 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 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, as these may increase the risk of adverse effects (see section 4.4).

Ibuprofen should be used with caution in combination with:

Corticosteroids: may increase the risk of adverse reactions, especially of the gastrointestinal tract (see section 4.4).

Antihypertensives and diuretics: NSAIDs may diminish the effects of these drugs. Diuretics can increase the risk of nephrotoxicity of NSAIDs.

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.

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. Serum digitalis concentrations should therefore be monitored in patients with decreased renal function or congestive heart failure.

Lithium: There is evidence for potential increase in plasma levels of lithium which may be clinically significant.

Methotrexate: There is the potential for increased plasma levels of 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.

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 of 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.

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 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 gastrochisis 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.

Lactation

Ibuprofen appears in breast milk in very low concentrations, and is unlikely to affect the breast fed infant adversely.

See section 4.4 regarding female fertility

4.7 Effects on ability to drive and use machines

None.

4.8 Undesirable effects

Hypersensitivity reactions have been reported and these may consist of:
a) Non-specific allergic reactions and anaphylaxis,
b) Respiratory tract reactivity comprising asthma, aggravated asthma, bronchospasm or dyspnoea,
c) Various skin reactions, e.g. pruritus, urticaria, angioedema and more rarely, exfoliative and bullous dermatoses (including epidermal necrolysis and erythema multiforme).

The list of the following adverse effects relates to those experienced with ibuprofen at OTC doses, from short-term use. In chronic conditions, under long-term treatment, additional adverse effects may occur. The most commonly-observed adverse events are gastrointestinal in nature.

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).

| Blood and lymphatic disorders | Very rare: | Haematopoietic disorders (anaemia, hemolytic anemia, aplastic anemia), leucopenia, thrombocytopenia, pancytopenia, agranulocytosis). First signs are: fever, sore throat, superficial mouth ulcers, flu-like symptoms, severe exhaustion, nose and skin bleeding, unexplained bleeding and bruising. |
| Immune system disorders | Uncommon: | Hypersensitivity reactions with urticaria and pruritus. |
| | Very rare: | 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. |
Severe hypersensitivity reactions. Symptoms could be:
facial, tongue and larynx swelling, dyspnoea,
tachycardia, hypotension, (anaphylaxis, angioedema or
severe shock).
Exacerbation of asthma and bronchospasm.

Not known: Non-specific allergic reactions, Various skin reactions
including exfoliative and bullous dermatoses (including
epidermal necrolysis and erythema multiforme).

<table>
<thead>
<tr>
<th>Psychiatric disorders</th>
<th>Very rare:</th>
<th>Nervousness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervous System</td>
<td>Uncommon:</td>
<td>Headache, dizziness, cerebrovascular accident</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Very rare:</td>
<td>Aseptic meningitis</td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td>Very rare:</td>
<td>Tinnitus and vertigo</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Very rare:</td>
<td>Cardiac failure, angina pectoris</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Very rare:</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Very rare:</td>
<td>Asthma, broncospasm, dyspnoea and wheezing</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Uncommon:</td>
<td>Abdominal pain, abdominal distension dyspepsia and nausea.</td>
</tr>
<tr>
<td></td>
<td>Rare:</td>
<td>Diarrhoea, flatulence, constipation and vomiting</td>
</tr>
<tr>
<td></td>
<td>Very rare:</td>
<td>Peptic ulcer, perforation or gastrointestinal haemorrhage, melaena, haematemesis, sometimes fatal, particularly in the elderly (see section 4.4). Exacerbation of ulcerative colitis and Crohn's disease (see section 4.4), ulcerative stomatitis, gastritis, Mouth ulceration.</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>Very rare:</td>
<td>Liver disorders, especially in long-term treatment, hepatitis and jaundice</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Uncommon:</td>
<td>Various skin rashes</td>
</tr>
<tr>
<td></td>
<td>Very rare:</td>
<td>Severe forms of skin reactions such as bullous reactions, including Stevens-Johnson Syndrome, erythema multiforme and epidermal necrolysis can occur.</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Very rare:</td>
<td>Acute renal failure, papillary necrosis, especially in long-term use, associated with increased serum urea and oedema. Haematuria, interstitial nephritis, nephritic syndrome, proteinuria.</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Very rare:</td>
<td>Oedema, swelling and peripheral oedema</td>
</tr>
<tr>
<td>Investigations</td>
<td>Very rare:</td>
<td>Decreased hematocrit and hemoglobin levels</td>
</tr>
<tr>
<td>Infections and Infestations:</td>
<td>Not known:</td>
<td>Meningitis</td>
</tr>
</tbody>
</table>

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) (see section 4.4).

### 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 vertigo, headache, respiratory depression, dyspnoea, drowsiness, occasionally excitation and
disorientation or coma. Occasionally patients develop convulsions. In serious poisoning, hypotension, hyperkalaemia, 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 – should be symptomatic and supportive and include 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: M01AE

Ibuprofen is a phenylpropionic 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. Single-dose clinical studies demonstrate that the pain relieving effects of ibuprofen liquigelss are evident within around 30 minutes of dosing. The effects of a 400mg dose of ibuprofen liquigelss are statistically superior to 1000mg paracetamol tablets both in the speed of onset and extent of analgesia. The differences in onset (see table below) are between 0.6 and 14 min. Ibuprofen 400mg pain relieving effects can last for up to 8 hours.

<table>
<thead>
<tr>
<th>Clinical Parameters</th>
<th>Ibuprofen Liquigels 200mg</th>
<th>Ibuprofen Liquigels 400mg</th>
<th>Acetaminophen 1g (2 x 500mg)</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Packman et al</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Total Pain Relief (TOTPAR)</td>
<td>N/A</td>
<td>15.2</td>
<td>12.2</td>
<td>5.8</td>
</tr>
<tr>
<td>Sum of Pain Relief &amp; Pain Intensity Difference (SPID)</td>
<td>N/A</td>
<td>39</td>
<td>53</td>
<td>&gt;180</td>
</tr>
<tr>
<td>Time to Meaningful Relief (mins)</td>
<td>N/A</td>
<td>39</td>
<td>53</td>
<td>&gt;180</td>
</tr>
<tr>
<td>Hersch et al</td>
<td>14.72</td>
<td>16.56</td>
<td>11.99</td>
<td>5.25</td>
</tr>
<tr>
<td>Total Pain Relief (TOTPAR)</td>
<td>6.93</td>
<td>8.07</td>
<td>5.05</td>
<td>0.46</td>
</tr>
<tr>
<td>Sum of Pain Relief &amp; Pain Intensity Difference (SPID)</td>
<td>30.0</td>
<td>28.8</td>
<td>29.4</td>
<td>&gt;360</td>
</tr>
<tr>
<td>Time to Meaningful Relief (mins)</td>
<td>30.0</td>
<td>28.8</td>
<td>29.4</td>
<td>&gt;360</td>
</tr>
<tr>
<td>Olson et al</td>
<td>N/A</td>
<td>17.42</td>
<td>13.30</td>
<td>4.33</td>
</tr>
<tr>
<td>Total Pain Relief (TOTPAR)</td>
<td>N/A</td>
<td>11.77</td>
<td>8.36</td>
<td>2.60</td>
</tr>
<tr>
<td>Sum of Pain Relief &amp; Pain Intensity Difference (SPID)</td>
<td>N/A</td>
<td>11.77</td>
<td>8.36</td>
<td>2.60</td>
</tr>
</tbody>
</table>
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 aspirin 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 ibuprofen use.

### 5.2 Pharmacokinetic properties

Ibuprofen is rapidly absorbed following administration and is rapidly distributed throughout the whole body. Compared to standard tablet formulations, ibuprofen administered in liquid-filled capsules reaches maximum plasma concentrations significantly faster. Peak plasma concentrations were achieved in around 35 minutes for liquiGels compared to around 90 minutes for standard ibuprofen tablets. 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 is about 2 hours. In limited studies, ibuprofen appears in 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

Capsule Contents:
- Macrogol 600
- Potassium hydroxide
Capsule shell:
- Sorbitol liquid, partially dehydrated (containing sorbitan and mannitol)
- Gelatin
- Purified water
Processing Aids:
- Ethanol solution
- Lecithin
- Triglycerides (medium chain)
Printing Ink:
Opacode black ink [iron oxide black (E172), propylene glycol, polyvinyl acetate phthalate (PVAP),
macrogol 400].

6.2 Incompatibilities

None known.

6.3 Shelf Life

3 years

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.

6.5 Special precautions for disposal and other handling

No special instructions

7. MANUFACTURER

WYETH LEDERLE S.R.L.
Via Nettunense 90,
Aprilia,
Italy

8. REGISTRATION HOLDER

Neopharm Ltd.
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POB 7063
Petach-Tiqva 49170
Israel

The format of this leaflet has been defined by the Ministry of Health; its content has been checked and
approved on February 2015.