Laboratorio Aldo-Unión, S.L.

C.I.F. B - 58364795

Baronesa de Maldá, 73 - P. O. Box 8
08950 ESPLUGUES DE LL. (Barcelona) ESPAÑA
Tel. 93 372 71 11 – Fax 93 371 61 98
Enlace Móvil 639 33 50 09
Web: http://www.aldo-union.com

SUMMARY OF PRODUCT CHARACTERISTICS FOR PHARMACEUTICALPRODUCTS

1. NAME OF THE MEDICINAL PRODUCT

PAIDOFEBRIL 100 mg/5 ml oral suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml of oral suspension contain: Ibuprofen (D.O.E.) 100 mg. For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Oral suspension.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Symptomatic treatment of slight to moderate pain
Symptomatic treatment of fever.
Treatment of juvenile rheumatoid arthritis.

4.2. Posology and method of administration

Children: The administered dose of ibuprofen depends on the age and weight of the child. For children aged 6 months up to 12 years, the daily recommended dose is 20 to 30 mg/kg of weight, divided into three or four doses. The interval between the doses will depend on the progress of the symptoms, but it should never be inferior to 4 hours.
For the treatment of juvenile rheumatoid arthritis greater doses might be needed, although it is recommended not to exceed 40 mg of ibuprofen per kg per day.
It is not recommended the use of ibuprofen in children younger than six months.
Adults and children older than 12: The recommended dose is 20 ml 3 to 4 times a day (equivalent to 1200-1600 mg of ibuprofen/day), while the symptoms persist.
Always take the minimum effective dose. The doctor will decide the duration of the treatment and it should not be interrupted before.
For patients with gastric discomfort, it is recommended to take the medicament during meals.
Old people: In general, no especial modifications are required in the dose, although it is recommended to administer ibuprofen with precaution, since these patients are generally more prone to suffer adverse effects.
Patients with renal failure: It is important to be careful when NSAID are used in patients with renal failure, as ibuprofen is eliminated preferably by this route. In patients with slight or moderate renal failure the initial dose should be reduced. Ibuprofen should not be used in patients with severe renal failure (See Contraindications).

Laboratorio Aldo-Unión, S.L.
C.I.F. B - 58364795
Baronesa de Maldá, 73 - P. O. Box 8
08950 ESPLUGUES DE LL. (Barcelona) ESPAÑA
Tel. 93 372 71 11 – Fax 93 371 61 98
Enlace Móvil 639 33 50 09
Web: http://www.aldo-union.com

Patients with hepatic failure: Although no differences have been observed in the ibuprofen pharmacokinetic profile in patients with hepatic failure, it is recommended to take precautions with the use of NSAID in this kind of patients. Patients with slight or moderate hepatic failure should start the treatment with small doses and they should be carefully monitorized. Ibuprofen should not be used in patients with severe hepatic failure (See Contraindications).

4.3. Method of administration

This medicament is administered by the oral route.
For a precise dosage, cans contain a 5 ml graduated oral syringe.

4.4. Contraindications

Known hypersensitivity to ibuprofen, other NSAID or any of the excipients of the formulation. Patients who have suffered attacks of asthma, acute rhinitis, urticaria, angioneurotic edema or other allergic reactions after the use of substances of similar action (for example acetylsalicylic acid or other NSAID).
Gastrointestinal haemorrhage.
Active peptic ulcer.
Intestinal inflammatory disease.
Severe renal dysfunction.
Severe hepatic dysfunction.
Patients with haemorrhagic diathesis or other coagulation disorders.
Pregnancy (See Pregnancy and lactation).

4.5. Special warnings and precautions for use

It is recommended precaution in patients with gastrointestinal disease, ulcerative colitis, Crohn's disease and alcoholism. Due to the possible appearance of digestive disorders, especially gastrointestinal bleeding, a careful monitorization of these patients should be carried out when ibuprofen or other NSAID are administered to them.
Should hemorrhage or gastrointestinal ulcer occur in patients treated with ibuprofen the treatment should be suspended immediately (see Contraindications).
In general, the consequences of the gastrointestinal hemorrhages or ulcers/perforations are more serious in old patients and they can occur at any time of the treatment with or without warning symptoms or a history of serious gastrointestinal incidents.
As it happens with other NSAID, allergic reactions, such as anaphylactic/anaphylactoid reactions, may also occur without previous exposure to the medicament.
Ibuprofen should be used with precaution in patients with a history of heart failure, hypertension, pre-existent edema due to any other reason and patients with hepatic o renal disease and especially during the simultaneous treatment with diuretics, since it should be taken into account that the inhibition of prostaglandins may induce liquids retention and impairment of the renal function. Should it be administered to these patients, the dose of ibuprofen should be maintained as low as possible, and the renal function should be monitored regularly.

Laboratorio Aldo-Unión, S.L.
C.I.F. B - 58364795
Baronesa de Maldá, 73 - P. O. Box 8
08950 ESPLUGUES DE LL. (Barcelona) ESPAÑA
Tel. 93 372 71 11 – Fax 93 371 61 98
Enlace Móvil 639 33 50 09
Web: http://www.aldo-union.com

In elderly patients, ibuprofen should be administered with precaution, as they are usually prone to suffer the side effects of NSAID.
NSAID may mask the symptoms of the infections.
It should be also administered with precaution in patients who suffer or have suffered frombronchial asthma, since NSAID may induce bronchospasm in this kind of patients (See Contraindications).
As it happens with other NSAID, ibuprofen may produce slight transitory increases in some hepatic parameters, as well as significant increases in SGOT and in SGPT. Should an important increase in these parameters occur, the treatment should be discontinued (See administration and dosage and Contraindications).
As it happens with other NSAID, ibuprofen may inhibit in a reversible way the aggregation and function of blood platelets, and prolong the hemorrhage time. It is recommended precaution when ibuprofen is administered concomitantly with oral anticoagulants.
In patients having long-term treatments with ibuprofen the renal function, hepatic function, hematological function and haematic count should be controlled as a preventive measure.
Warning about excipients:
This medicament contains maltitol syrup, so patients with rare hereditary problems of fructose intolerance should not take this medicament.

4.6. Paediatric population

The administered dose of ibuprofen depends on the age and weight of the child. For children aged 6 months up to 12 years, the daily recommended dose is 20 to 30 mg/kg of weight, divided into three or four doses. The interval between the doses will depend on the progress of the symptoms, but it should never be inferior to 4 hours.
For the treatment of juvenile rheumatoid arthritis greater doses might be needed, although it is recommended not to exceed 40 mg of ibuprofen per kg per day.
It is not recommended the use of ibuprofen in children younger than six months.

4.7. Interaction with other medicinal products and other forms of interaction

In general, NSAID should be used with precaution when they are used with other drugs that may increase the risk of gastrointestinal ulceration, gastrointestinal hemorrhage or renal dysfunction.
It is not recommended its concomitant use with:
- Other NSAID: It should be avoided the simultaneous use with other NSAID, since the administration of different NSAID may increase the risk of gastrointestinal ulcer and hemorrhages.
- Methotrexate administered at doses of 15 mg/week or greater: If NSAID and methotrexate are administered within an interval of 24 hours, an increase in the plasmatic level of methotrexate may occur (apparently, its renal clearance may be reduced by the effect of NSAID), with the resulting increase in the risk of toxicity by methotrexate. As a result of it, it should be avoided the use of ibuprofen in patients who are being treated with methotrexate at high doses.
- Hydantoins and sulphamides: The toxic effects of these substances may be increased.
- Ticlopidine: NSAID should not be combined with ticlopidine due to the risk of an additive effect in the inhibition of the function of blood platelets.

Laboratorio Aldo-Unión, S.L.
C.I.F. B - 58364795
Baronesa de Maldá, 73 - P. O. Box 8
08950 ESPLUGUES DE LL. (Barcelona) ESPAÑA
Tel. 93 372 71 11 – Fax 93 371 61 98
Enlace Móvil 639 33 50 09
Web: http://www.aldo-union.com

- Lithium: NSAID may increase the lithium plasmatic levels, possibly due to the reduction of its renal clearance. Its concomitant administration should be avoided, unless the lithium levels are monitorized. It should be considered the possibility of reducing the dose of lithium.
- Anticoagulant drugs: NSAID may reinforce the effects of the anticoagulant drugs on the bleeding time. Therefore, the simultaneous use of these drugs should be avoided. Should this not be possible, coagulation tests should be carried out at the beginning of the treatment with ibuprofen, and, if necessary, the dose of the anticoagulant drug should be adjusted.
- Mifepristone: Non-steroidal antiinflammatory drugs should not be administered in a period of 8-12 days after the administration of mifepristone since they may reduce its effects.

It is recommended precaution with:

- Digoxin: NSAID may raise the plasmatic levels of digoxin, increasing this way the risk of toxicity by digoxin.
- Cardiac Glycosides: Non-steroidal antiinflammatory drugs may aggravate heart failure, reduce the glomerular filtration rate and increase the levels of cardiac glycosides.
- Methotrexate administered at low doses, smaller than 15 mg/week: Ibuprofen increases the levels of methotrexate. When it is used in combination with methotrexate at low doses, the haematic values of the patient should be strictly monitorized, mainly during the first weeks of simultaneous administration. It will be also necessary to increase the monitorization in the case of deterioration of the renal function, however minimum it is, and in old patients, as well as to monitorize the renal function in order to prevent a possible reduction in the methotrexate clearance.
- Pentoxyphiline: In patients who are being treated with ibuprofen in combination with pentoxyphiline it may increase the risk of hemorrhage, so it is recommended to monitorize the bleeding time.
- Phenytoin: During the simultaneous treatment with ibuprofen the plasmatic levels of phenytoin could be increased.
- Probenecid and sulphinpyrazone: May cause an increase in the plasmatic concentrations of ibuprofen; this interaction can be due to an inhibitor mechanism in the spot where the tubular renal secretion and the glucuronoconjugation are produced, and it could require adjusting the dose of ibuprofen.
- Quinolones: Isolated cases of seizures that could have been caused by the simultaneous use of quinolones and certain NSAID have been reported.
- Tiazides, substances related with tiazides, loop diuretics and potassium saver diuretics: NSAID may counteract the diuretic effect of these drugs, and the simultaneous use of a NSAID and a diuretic may increase the risk of renal failure as a result of a reduction in the renal blood flow. As ithappens with other NSAID, the concomitant treatment with potassium saver diuretics may be associated to an increase in the potassium levels, so it is necessary to monitorize the plasmaticlevels of this ion.
- Sulfonylureas: NSAID may reinforce the hypoglycemic effect of sulfonylureas, displacing them from their binding to plasmatic proteins.
- Cyclosporine, tacrolimus: Their simultaneous administration with NSAID may increase the riskof nephrotoxicity due to the reduction of the renal synthesis of prostaglandins. Should they be

Laboratorio Aldo-Unión, S.L.
C.I.F. B - 58364795
Baronesa de Maldá, 73 - P. O. Box 8
08950 ESPLUGUES DE LL. (Barcelona) ESPAÑA
Tel. 93 372 71 11 – Fax 93 371 61 98
Enlace Móvil 639 33 50 09
Web: http://www.aldo-union.com

administered concomitantly, the renal function should be closely monitored.

- Corticosteroids: The simultaneous administration of NSAID and corticosteroids may increase the risk of gastrointestinal ulcer.
- Antihypertensive drugs (including ECA inhibitors or beta-blockers): NSAID-type anti-inflammatory drugs may reduce the effectiveness of the antihypertensive drugs. The simultaneous treatment with NSAID and ECA inhibitors can be associated to the risk of acute renal failure.
- Thrombolytic drugs: They may increase the risk of hemorrhage.
- Zidovudine: It may increase the risk of toxicity on the red blood cells through the effect on the reticulocytes, appearing serious anemia to week after the commencement of the administration of NSAID. During the simultaneous treatment with NSAID the haematic values should be monitorized, mainly at the beginning of the treatment.

Food: The administration of ibuprofen together with food retards the speed of absorption (See Pharmacokinetic properties).

4.8. Additional information on special populations

4.9. Fertility, pregnancy and lactation

Despite there have not been detected teratogenic effects in the toxicity studies conducted on animals after the administration of ibuprofen; its use should be avoided during pregnancy.

NSAID are contraindicated specially during the last three months of pregnancy. They can inhibit labor and delay the delivery. They can cause the premature closure of ductus arteriosus, causing lung hypertension and respiratory failure in the newborn. They can alter the fetal function of the blood platelets and also the renal function of the foetus, giving rise to a deficiency of amniotic fluidand neonatal anuria.

Despite the fact that the concentrations of ibuprofen that reach mother's milk are invaluable and no undesirable effects are expected in nursing infants, the use of ibuprofen is not recommended in the lactation period due to the potential risk of inhibiting the synthesis of prostaglandins in the newborn.

4.10. Effects on ability to drive vehicles and use machines

Patients who suffer dizziness, vertigo, visual disturbances or other central nervous system disorders should refrain from driving or operating machinery while they are taking ibuprofen.

If it is administered a single dose of ibuprofen or for a short period of time, it is not necessary to take special precautions.

4.11. Undesirable effects

Gastrointestinal:

Very frequent (more than 1/10): dyspepsia, diarrhoea.

Frequent (more than 1/100, less than 1/10): nausea, vomits, and abdominal pain.

Less frequent (more than 1/1.000, less than 1/100): hemorrhages and gastrointestinal ulcers,ulcerous stomatitis.

Laboratorio Aldo-Unión, S.L.
C.I.F. B - 58364795
Baronesa de Maldá, 73 - P. O. Box 8
08950 ESPLUGUES DE LL. (Barcelona) ESPAÑA
Tel. 93 372 71 11 – Fax 93 371 61 98
Enlace Móvil 639 33 50 09
Web: http://www.aldo-union.com

Rare (less than 1/1.000): gastrointestinal perforation, flatulence, constipation, esophagitis,esophageal stenosis, diverticular disease aggravation, unspecific hemorrhagic colitis, ulcerous colitis or Crohn's disease.
Should gastrointestinal hemorrhage occur, it could cause anemia and haematemesis.
Skin reactions and hypersensitivity reactions:
Frequent: Rash.
Less frequent: urticaria, pruritus, purpura (allergic purpura included), angioedema, rhinitis and bronchospasm.
Rare: anaphylactic reaction.
Very rare: (less than 1/10.000): erythema multiforme, epidermal necrolysis, systemic lupus erythematosus, alopecia, photosensitivity reactions, serious skin reactions such as Stevens-Johnson syndrome, acute toxic epidermal necrolysis (Lyell syndrome) and allergic vasculitis.
The majority of the cases in which aseptic meningitis with ibuprofen has been reported, the patient suffered any kind of autoimmunitary disease (such as systemic lupus erythematosus or other collagen diseases), which meant a risk factor. In the event of a serious generalized hypersensitivity reaction, face, tongue and larynx swelling, bronchospasm, asthma, tachycardia, hypotension and shock may appear.
Central nervous system:
Frequent: fatigue or somnolence, headache, dizziness, vertigo.
Less frequent: insomnia, anxiety, restlessness, visual disorders, and tinnitus.
Rare: psychotic reaction, nervousness, irritability, depression, confusion or disorientation,reversible toxic amblyopy, ear disorders.
Very rare: aseptic meningitis (see hypersensitivity reactions).
Hematological:
The bleeding time may be prolonged. The rare cases of hematological disorders observed correspond to thrombocytopenia, leukopenia, granulocytopoenia, pancytopenia, agranulocytosis, aplasic anemia or hemolytic anemia.
Cardiovascular:
Patients with hypertension or renal disorders are apparently more likely to suffer hydric retention. Hypertension or heart failure may occur (especially in old patients).
Renal:
Basing on the experience with NSAID in general, cases of interstitial nephritis, nephrotic syndrome and renal failure cannot be excluded.
Hepatic:
In rare cases anomalies in the hepatic function, hepatitis and jaundice with racemic ibuprofen have been observed.
Other:
In very rare cases inflammations associated to infections could be aggravated.

4.12. Overdose
The majority of the cases of overdosage they have been asymptomatic. There is a risk of symptoms

Laboratorio Aldo-Unión, S.L.
C.I.F. B - 58364795
Baronesa de Maldá, 73 - P. O. Box 8
08950 ESPLUGUES DE LL. (Barcelona) ESPAÑA
Tel. 93 372 71 11 – Fax 93 371 61 98
Enlace Móvil 639 33 50 09
Web: http://www.aldo-union.com

with doses greater than 80-100 mg /kg of ibuprofen.

The appearance of the overdosage symptoms takes place normally in a period of 4 hours. The slight symptoms are the most frequent, and they include abdominal pain, nausea, vomiting, lethargy, somnolence, headache, nystagmus, tinnitus and ataxia. Rarely moderate or intense symptoms have appeared, such as gastrointestinal hemorrhage, hypotension, hypothermia, metabolic acidosis, seizures, renal function disturbance, coma, respiratory distress in adults and transitory episodes of apnea (in children after the ingestion of big quantities).
The treatment is symptomatic and there is no specific antidote. For quantities that are not likely to produce symptoms (less than 50 mg/kg of ibuprofen) water can be administered to reduce gastrointestinal troubles to the maximum. In the event of ingestion of considerable quantities, activated charcoal should be administered. The gastric lavage by means of emesis should only be considered during the 60 minutes after the ingestion. So, gastric lavage should not be considered, unless the patient has ingested a quantity of the drug that may endanger the patient's life and that there have not passed more than 60 minutes after the ingestion of the medicament. The benefit of measures such as forced diuresis; hemodialysis or hemoperfussion proves to be doubtful, since ibuprofen binds strongly to plasmatic proteins.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmaceutical group: non-steroidal anti-inflammatory drug.
Ibuprofen is a non-steroidal compound by-product of propionic acid with strong anti-inflammatory, analgesic, and antipyretic properties.
Its mechanism of action may be due to the inhibition of the prostaglandins synthesis. Prostaglandins play an essential part in the appearance of fever, pain and inflammation.

5.2. Pharmacokinetic properties

Ibuprofen is a drug that has linear-type pharmacokinetics.
Absorption:
Ibuprofen administered by the oral route is quickly absorbed in a proportion of approximately 80% in the gastrointestinal tract. The maximum plasmatic concentrations are reached 1-2 hours after the administration.
Distribution:
The apparent distribution volume of ibuprofen after the oral administration is 0,1 to 0,2 L/kg, with a strong binding to plasmatic proteins of about 99%.
Metabolism:
Ibuprofen is extensively metabolized in the liver by hydroxylation and carboxylation of the isobutyl group and its metabolites lack pharmacological activity.
Elimination:
The elimination of ibuprofen takes place mainly at renal level and it is considered to be complete after 24 hours. Approximately 10% is eliminated unaltered and a 90% is eliminated in the form of

Laboratorio Aldo-Unión, S.L.
C.I.F. B - 58364795
Baronesa de Maldá, 73 - P. O. Box 8
08950 ESPLUGUES DE LL. (Barcelona) ESPAÑA
Tel. 93 372 71 11 – Fax 93 371 61 98
Enlace Móvil 639 33 50 09
Web: http://www.aldo-union.com

inactive metabolites, mainly as glucuronids.

The administration of ibuprofen together with food delays the Tmax (from ± 2 h fasting to ± 3 h after eating), although this does not have any effect on the magnitude of the absorption.

5.3. Preclinical safety data

Ibuprofen did not prove to be teratogenic in various animal species. In the same way, both the mutagenesis and the carcinogenesis studies produced negative results.
In some animal reproduction studies, it has been observed an increase in the dystocias and delays in delivery, related with the inhibitor action characteristic of the prostaglandins synthesis of the NSAID.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Glycerol, maltitol syrup, microcrystalline cellulose, xanthane gum, anhydrous citric acid, sodium citrate, Sodium benzoate (E211), polysorbate 80, sodium saccharine, orange essence and purified water.

6.2. Incompatibilities

None known.

6.3. Shelf life

3 years
Special precautions of storage

6.4. Special precautions for storage

No special precautions of storage are needed.

6.5. Nature and contents of container

200 ml bottle, with 5 ml syringe for oral dosage

6.6. Special precautions for disposal and other handling

None.

7. MARKETING AUTHORIZATION HOLDER AND MANUFACTURING SITE ADDRESS:

Laboratorio ALDO-UNIÓN, S.L.
Baronesa de Maldá, 73
08950 Esplugues de Llobregat
BARCELONA – SPAIN

Laboratorio Aldo-Unión, S.L.

C.I.F. B - 58364795

Baronesa de Maldá, 73 - P. O. Box 8
08950 ESPLUGUES DE LL. (Barcelona) ESPAÑA
Tel. 93 372 71 11 – Fax 93 371 61 98
Enlace Móvil 639 33 50 09
Web: http://www.aldo-union.com

8. MARKETING AUTHORISATION NUMBER

To be included after obtaining first registration.

9. DATE OF FIRST REGISTRATION/RENEWAL OF THE REGISTRATION

It will be applicable after registration of this product.

10. DATE OF REVISION OF THE TEXT
