Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Provin 100 mg / 5 ml Oral Suspension

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Ibuprofen 100 mg/5ml.

Excipients with known effect :
Sodium methylhydroxybenzoate (E219) - 9mg per 5ml
Sodium propylhydroxybenzoate (E217) - 1mg per 5ml
Maltitol - 1ml per 5ml

For the full list of excipients - see section 6.1.

3 PHARMACEUTICAL FORM

Oral Suspension
White, uniform suspension.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Ibuprofen 100 mg/5 ml Oral Suspension is used as an analgesic for relief of mild to moderate muscular pain, symptomatic relief of headache, earache, dental pain and backache. It can also be used in minor injuries such as sprains and strains. Ibuprofen 100 mg/5 ml Oral Suspension is effective in the relief of feverishness and symptoms of colds and influenza.

4.2 Posology and method of administration

For oral administration and short-term use only.

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.4).

Children:

Not recommended for children weighing less than 5 kg.

For pain and fever - 20mg/kg/day in divided doses

Infants 3-6 months weighing more than 5kg:	One 2.5ml dose may be taken 3 times in 24 hours
Infants 6-12 months:	2.5ml three times a day.
Children 1-2 years:	2.5ml three to four times a day
Children 3-7 years:	5ml three to four times a day
Children 8-12 years:	10ml three to four times a day.

A minimum of 4 hours can be left between each dose.
Do not use more than 4 times a day.

Do not give to children under 3 months of age.

For infants aged 3-5 months medical advice should be sought if symptoms worsen or not later than 24 hours if symptoms persist. If in children aged from 6 month this medicinal product is required for more than 3 days, or if symptoms worsen a doctor should be consulted.

4.3 Contraindications

Hypersensitivity to the active substance 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 aspirin or other non-steroidal anti-inflammatory drugs.

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's therapy.

Severe heart failure (NYHA Class IV).

Severe hepatic failure or renal failure (see section 4.4, Special Warnings and precautions for use).

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 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.

Provin Oral Suspension contains:

- Sodium methylhydroxybenzoate (E219) and sodium propylhydroxybenzoate (E217) – may cause allergic reactions which could possibly be delayed.
- Maltitol – Patients with rare hereditary problems of fructose intolerance should not take this medicine. Maltitol may have a mild laxative effect. Calorific value 2.3kcal/g maltitol. Each 5ml of Provin contains 1ml of maltitol liquid.

SLE and mixed connective tissues disease:
Systemic lupus erythematosus and mixed connective tissue disease-increased risk of aseptic meningitis (see section 4.8 Undesirable effects).

Ibuprofen inhibits platelet aggregation and prolongs bleeding time, although the effect is less pronounced than that seen with aspirin. Ibuprofen should be used with caution in patients with coagulation defects and those on anticoagulant therapy.

Respiratory:
Ibuprofen should be used with caution in patients suffering from or with a previous history of bronchial asthma or allergic disease, since such patients may have NSAID – sensitive asthma which has been associated with precipitating severe bronchospasm.

Cardiovascular and cerebrovascular effects:
Caution (discussion with doctor of 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. NSAIDs should be used with caution in patients with fluid retention and in patients taking a diuretic.

Clinical studies suggest that use of ibuprofen, particularly at a high dose (2400mg/day) may be associated with a small

increased risk of arterial thrombiotic 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 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, smoking), particularly if high doses of ibuprofen (2400 mg/day) are required.

Ibuprofen may decrease the cardioprotective and antiplatelet activity of aspirin (see section 4.5).

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. The use of Ibuprofen is therefore not recommended in women attempting to conceive.

Gastrointestinal:
NSAIDs should be given with care to patients with a history of gastrointestinal disease (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 anytime during treatment, with or without warning symptoms or a previous history of serious GI events.

The risk of GI bleeding with NSAIDs increases with dose and duration of use, and may be higher in patients with a history of gastric ulcers, particularly if complicated with haemorrhage or perforation (see section 4.3); in patients with a history of bleeding disorders; with alcohol use - 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 other NSAIDs, 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 occur in patients receiving ibuprofen the treatment should be withdrawn.

Renal, Hepatic and Cardiac Impairment:
Administration of NSAIDs such as Ibuprofen may cause dose dependent renal toxicity in patients with reduced renal blood flow or blood volume where renal prostaglandins support the maintenance of renal perfusion.
Patients at risk of this reaction include those with impaired renal function, heart failure or liver dysfunction. This is of particular importance in hypertension and/or cardiac impairment as renal function may deteriorate and/or fluid retention occur. Caution is therefore required in the use of Ibuprofen in such patients.

Other NSAIDs:
The use of Ibuprofen 100mg/5ml Oral Suspension with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided (see section 4.5 Interactions).

Immune System and Dermatological:

Ibuprofen may cause a severe allergic reaction, especially in patients allergic to aspirin. Symptoms may include hives, facial swelling, asthma (wheezing), shock, skin reddening, rash or blisters. If any of these symptoms occur, patients should stop use and seek medical help right away.

Serious skin reactions, some of them fatal, including exfoliative dermatitis, erythema multiforme, Stevens-Johnson

syndrome and toxic epidermal necrolysis, have been reported 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 100mg/5ml Oral Suspension should be discontinued at the first appearance of skin rash, mucosal lesions or any other sign of hypersensitivity.

Exceptionally, varicella can be at the origin of serious cutaneous and soft tissue infectious complications. To date, the contributing role of NSAIDs in the worsening of these infections cannot be ruled out. Thus, it is advisable to avoid use of Ibuprofen 100mg/5ml Oral Suspension in case of varicella.

Not recommended for children under 3 months.

There is a risk of renal impairment in dehydrated children and adolescents.

The label will include:
Read the package leaflet before use.

Do not give this product if your baby or child
- Has (or has had two or more episodes of) a stomach ulcer, perforation or bleeding
- Is allergic to ibuprofen or any other ingredient of the product, aspirin or other related painkillers
- Is taking other NSAIDs painkillers, or aspirin with a daily dose above 75 mg

Speak to a pharmacist or your doctor before giving this product if your baby or child
- Has or has ever had asthma, diabetes, high blood pressure, high cholesterol a stroke liver, heart, kidney or bowel problems or is dehydrated.

If you are an adult taking this product you should not take it in the last 3 months of pregnancy and you should contact your doctor or pharmacist before taking in the first 6 months of pregnancy, if you are trying to get pregnant, if you are elderly or if you are a smoker.

Do not give to babies aged 3-6 months for more than 24 hours.

Do not give to children aged 6 months and older for more than 3 days.

If symptoms persist or worsen or if new symptoms occur, consult your doctor promptly.

Do not exceed the stated dose.

Not recommended for children under 3 months.

4.5 Interaction with other medicinal products and other forms of interaction

Ibuprofen should be avoided in combination with:

Acetylsalicylic acid
Concomitant administration of ibuprofen and acetylsalicylic acid 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 acetylsalicylic acid 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 acetylsalicylic acid cannot be excluded. No clinically relevant effect is considered to be likely for occasional ibuprofen use (see section 5.1).

Other NSAIDs: including cyclo-oxygenase-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 anticoagulants such as warfarin (see section 4.4).

Because bleeding has been reported when ibuprofen and other NSAIDs have been administered to patients on coumarin-type anticoagulants, and because the NSAID class carries a potential for gastrointestinal bleeding, caution should be taken if ibuprofen is used by patients also taking anticoagulants.

However, several short-term controlled studies failed to show that ibuprofen significantly affected prothrombin times or a variety of other clotting factors when administered to individuals on coumarin-type anticoagulants.

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

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

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

Methotrexate: There is potential for an increase in plasma 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 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.

Alcohol : Alcohol use may increase the risk of gastrointestinal bleeding when taking drugs in the NSAID class, including ibuprofen. Therefore, caution should be taken when using ibuprofen with alcohol.

4.6 Fertility, pregnancy and lactation

Whilst no teratogenic effects have been demonstrated in animal experiments the use of Ibuprofen 100mg/5ml Oral Suspension, should if possible, be avoided during the first 6 months of pregnancy.

During the 3rd trimester, ibuprofen is contraindicated as there is a risk of premature closure of the foetal ductus arteriosus with possible persistent pulmonary hypertension. The onset of labour may be delayed and the duration increased with an increased bleeding tendency in both mother and child (see section 4.3 Contraindications).

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

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

Hypersensitivity reactions have been reported and these may consist of :

a. Non-specific allergic reactions including severe hypersensitivity reactions. Symptoms could be facial, tongue and laryngeal swelling, dyspnoea, tachycardia, hypotension (anaphylaxis, angioedema or severe shock)

b. Respiratory tract reactions of 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).

Clinical studies suggest that use of ibuprofen, particulary at a high dose (2400 mg/day) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke) (see Section 4.4).

The adverse reactions observed in patients treated with ibuprofen during clinical trials and post-marketing experience are listed below by system organ class. Frequencies are defined in accordance with current guidance as:
Very common (≥1/10)
Common (≥1/100 and <1/10)
Uncommon (≥1/1,000 and <1/100)
Rare (≥1/10,000 and <1/1.000)
Very rare (<1/10,000)
Not known frequency (cannot be estimated from the available data).

ADRs are presented by frequency category based on 1) incidence in adequately designed clinical trials or epidemiology studies, when available, or 2) when incidence is unavailable, frequency category is listed as ‘Not known.

Body system (SOC)	**Incidence**	**Adverse Event Preferred Term**
Infections and infestations	Rare	Meningitis aseptic+
- Blood & lymphatic system disorders	Rare	Agranulocytosis
	Rare	Anaemia
	Rare	Eosinophilia
	Rare	Leucopenia
	Rare	Pancytopenia
	Rare	Thrombocytopenia
Immune system disorders	Uncommon	Angioedema
	Uncommon	Hypersensitivity (with urticaria and pruritus)
	Rare	Anaphylactic reaction**
Nervous system disorders	Common	Dizziness¥
	Common	Headache
	Common	Somnolence#¥
	Rare	Cerebrovascular accident*
	Rare	Psychomotor hyperactivity (including Agitation, Anxiety and Nervousness)

Eye disorders	Rare	Vision blurred
	Rare	Visual impairment (including Amblyopia)
Cardiac disorders	Rare	Cardiac failure*
	Rare	Myocardial infarction*
Vascular disorders	Uncommon	Bleeding (Non-GI)
	Rare	Hypertension
Respiratory, thoracic and mediastinal disorders	Rare	Asthma
	Rare	Bronchospasm
Gastrointestinal disorders	Common	Abdominal pain¥
	Common	Dyspepsia¥
	Common	Nausea
	Common	Vomiting
	Uncommon	Constipation
	Uncommon	Diarrhoea
	Rare	Flatulence
	Rare	Gastrointestinal haemorrhage** (including Haematemesis and Melaena)
	Rare	Gastrointestinal inflammation (including Colitis, Gastritis and Stomatitis)
	Rare	Gastrointestinal ulcer (including peptic ulcer)
	Rare	Gastrointestinal ulcer haemorrhage
	Rare	Gastrointestinal ulcer perforation**
	Rare	Oral discomfort (local burning sensation, irritation)
	Rare	Pancreatitis
	Very rare	Crohn's disease
Hepatobiliary disorders	Rare	Liver disorders***
Skin and subcutaneous tissue disorders	Uncommon	Pruritus
	Uncommon	Rash
	Rare	Erythema
	Rare	Erythema multiforme
	Rare	Stevens-Johnson Syndrome
	Rare	Toxic epidermal necrolysis
	Rare	Urticaria
Renal and urinary disorders	Rare	Nephritis
	Rare	Renal failure
	Rare	Renal impairment
	Rare	Renal papillary necrosis*~
General disorders and administration site conditions	Common	Asthenia¥
	Rare	Oedema

**Reported as NSAID class effect, not supported by company post-marketing ibuprofen data*
***Death/fatal outcome has been reported*
****More likely associated with greater than non-prescription doses*
 # AEs reported by ≥1% of ibuprofen-treated paediatric subjects in randomised placebo-controlled clinical trials

¥ AEs reported by ≥1% of ibuprofen-treated adult subjects in randomised placebo-controlled clinical trials
~ Especially in long term use
+ 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

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. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

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, abdominal 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 lethargy or drowsiness, occassionally excitation and disorientation or coma. Occasionally patients develop convulsions.

In serious poisoning (of more than 400 mg/kg) 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. Rhabdomyolysis, hypothermia and apnoea (primarily in very young children) may also rarely occur. Cardiovascular toxicity, including hypotension, bradycardia, tachycardia and atrial fibrillation have also been reported. The onset of symptoms usually occurs within 4 hours.

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

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 competitively inhibit the effect of low dose acetylsalicylic acid on platelet aggregation when they are dosed concomitantly. Some pharmacodynamic studies show that when single doses of ibuprofen 400mg was taken within 8 hours or within 30 minutes after immediate release acetylsalicylic acid dosing (81mg), a decreased effect of acetylsalicylic acid on the formation of thromboxane or platelet aggregation occurred. 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 acetylsalicylic acid cannot be excluded. No clinically relevant effect is considered to be likely for occasional ibuprofen use (see section 4.5).

5.2 Pharmacokinetic properties

Ibuprofen is rapidly absorbed following administration and is rapidly distributed throughout the whole body. Peak

plasma concentrations occur about 1 to 2 hours after ingestion with food or in 45 minutes if taken on an empty stomach. These times may vary with different dosage forms.

The excretion is rapid and complete via the kidneys.

The half life of Ibuprofen is about 2 hours.
In limited studies, ibuprofen appears in the breast milk in very low concentrations.

It is metabolised to two inactive metabolites and these are rapidly excreted in urine. About 1 percent is excreted in urine as unchanged Ibuprofen and about 14 percent as conjugated Ibuprofen.

5.3 Preclinical safety data

No relevant information additional to that contained elsewhere in the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycerol (E422)
Xanthan gum
Maltitol syrup (Lycasin 80/55 (E965)
Polysorbate 80
Saccharin sodium (E954)
Citric acid monohydrate
Sodium methyl hydroxybenzoate (E219)
Sodium propyl hydroxybenzoate (E217)
Purified water
Strawberry flavour

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25ºC.

6.5 Nature and contents of container

An amber glass bottle sealed with child resistant, tamper evident cap.
Pack sizes available: 50ml, 100ml and 150ml.

6.6 Special precautions for disposal

Shake well before use. Return any left over medicine to the Pharmacist.

7 MARKETING AUTHORISATION HOLDER

McNeil Healthcare (Ireland) Limited
Airton Road
Tallaght
Dublin 24

8 MARKETING AUTHORISATION NUMBER

PA0823/044/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26 May 2006
Date of last renewal: 22 March 2007

10 DATE OF REVISION OF THE TEXT

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