AUSTRALIAN PRODUCT INFORMATION – Advil® 12Hour Extended Release Tablet (Ibuprofen)

1. NAME OF THE MEDICINE

Each Advil®12Hour Extended Release Tablet (referred as Advil 12Hour) contains 600mg Ibuprofen.

The first layer consists of 200 mg ibuprofen immediate release and the second layer, 400 mg ibuprofen extended release.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Advil12Hour is a bi-layer tablet which contains 600 mg ibuprofen.

The first layer consists of 200 mg ibuprofen immediate release and the second layer, 400 mg ibuprofen extended release.

Also contains sulfites, soya beans and soya bean products.

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Advil 12Hour is a white, film-coated, capsule-shaped tablet printed in blue ink on one side.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Advil 12Hour is indicated for use as follows:

- Temporary relief of persistent pain likely to last for more than 6 hours associated with: body pain, back pain, neck and shoulder pain, muscle pain, sprains and strains, osteoarthritis, arthritic, joint and rheumatic conditions, period pain, dental pain, sinus pain, cold and flu.

4.2 DOSE AND METHOD OF ADMINISTRATION

Adults and children 12 years and over:
Take 1 tablet every 12 hours while symptoms persist. Swallow tablet whole with water - do not crush, chew, split or dissolve.

Do not take more than 1 tablet at a time.
Do not exceed 2 tablets in 24 hours.
Do not give this product to children under 12 years of age.

Advil 12Hour should not be used for more than a few days at a time unless on medical advice, in which case the patient should be reviewed regularly with regards to efficacy, risk factors and ongoing need for treatment.

Patient should be advised to stop use of this medicine and consult a doctor if pain worsens or lasts for more than a few days.

If the pain usually lasts less than 6 hours or pain is expected to last less than 6 hours,
Advil 12Hour should not be used. It is recommended to use regular Advil tablets or Advil liquid capsules.

4.3 CONTRAINDICATIONS

Advil 12Hour is contraindicated for use in:

- Patients with known hypersensitivity or idiosyncratic reaction to ibuprofen (or any of the other ingredients in the product).
- Patients with known hypersensitivity to aspirin and other NSAIDs.
- Patients with asthma that is aspirin or NSAID sensitive.
- Patients with active or previous history of gastrointestinal bleeding or ulceration.
- Pregnant women or women who are trying to become pregnant (see Precautions - 'Use in pregnancy').
- Patients with renal impairment.
- Patients with heart failure.
- Patients with severe liver impairment.
- Patients undergoing treatment of perioperative pain in setting of coronary artery bypass surgery (CABG).

Advil 12Hour should not be taken with other products containing ibuprofen or with other anti-inflammatory medicines.

Refer to 'Interactions with other medicines' for additional information.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Advil 12Hour should be used with caution in:

- Patients with asthma.
- Patients with cardiac impairment or hypertension (see 'Precautions - Cardiovascular and cerebrovascular effects').
- Patients with hepatic impairment (see 'Precautions - Hepatic').
- Patients taking other products containing aspirin and salicylates.

Ibuprofen may cause severe allergic reactions including skin reddening, rash, or blisters. Patients should be advised to stop use and immediately contact a doctor if these symptoms are observed.

Ibuprofen may cause a patient to vomit blood or have bloody or black stools. Patients should be advised to stop use and contact a doctor immediately if these symptoms are observed.

Side effects may be minimised by using this medicine for the shortest duration necessary to control symptoms.

Excessive or prolonged use can be harmful and increase the risk of heart attack, stroke or liver damage.

Use with caution in the elderly (see 'Use in the elderly').

Refer to 'Interactions with other medicines and other forms of interactions' for additional information.

Identified precautions

Cardiovascular and cerebrovascular effects

Observational studies have indicated that NSAIDs may be associated with an increased risk of serious cardiovascular events, including myocardial infarction and stroke, which may increase with dose or duration of use.

Patients with cardiovascular disease, history of atherosclerotic cardiovascular disease or cardiovascular risk factors may also be at greater risk.

Patients should be advised to remain alert for such cardiovascular events, even in the absence of previous cardiovascular symptoms. Patients should be informed about signs and/or symptoms of serious cardiovascular toxicity and the steps to take if they occur.

Fluid retention, hypertension and oedema have been reported in association with NSAID therapy. Patients taking antihypertensives with NSAIDs may have an impaired antihypertensive response.

Advil 12Hour should be used with caution in patients with hypertension (see also 'Contraindications' – heart failure).

Use in hepatic impairment

As with other NSAIDs, elevations of one or more liver function tests may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged or may resolve with continued therapy. Meaningful elevations (three times the upper limit of normal) of ALT or AST occurred in controlled clinical trials in less than 1% of patients.

Patients should be advised to remain alert for hepatotoxicity and be informed about the signs and/or symptoms of hepatotoxicity (e.g. nausea, fatigue, lethargy, pruritus, jaundice, abdominal tenderness in the right upper quadrant and "flu-like" symptoms).

Use in renal impairment

No data available.

Use in the elderly

Ibuprofen should not be taken by adults over the age of 65 without careful consideration of co-morbidities and co-medications because of an increased risk of adverse effects, in particular heart failure, gastro-intestinal ulceration and renal impairment (see also 'Contraindications' – renal impairment, heart failure).

Paediatric use

Advil 12Hour is not indicated for children <12 years of age.

Effects on laboratory tests

See section 4.8 Adverse effects (undesirable effects)

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

The following interactions with ibuprofen have been noted:

- Other NSAIDs.
- Anticoagulants, including warfarin – ibuprofen interferes with the stability of INR and may increase risk of severe bleeding and sometimes fatal haemorrhage, especially from the

gastrointestinal tract. Ibuprofen should only be used in patients taking warfarin if absolutely necessary and they must be closely monitored.

- Ibuprofen may decrease renal clearance and increase plasma concentration of lithium.
- Ibuprofen may reduce the anti-hypertensive effect of ACE inhibitors, beta-blockers and diuretics and may cause natriuresis and hyperkalaemia in patients under these treatments.
- Ibuprofen reduces methotrexate clearance.
- Ibuprofen may increase the plasma levels of cardiac glycosides.
- Ibuprofen may increase the risk of gastrointestinal bleeding especially if taken with corticosteroids.
- Ibuprofen may prolong bleeding time in patients treated with zidovudine.
- Ibuprofen may also interact with probenecid, antidiabetic medicines and phenytoin.
- Ibuprofen may decrease the benefit of aspirin taken for heart attack or stroke.
- Ibuprofen may increase the risk of gastrointestinal bleeding if combined with selective serotonin reuptake inhibitors (SSRIs).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No data available.

Use in pregnancy – Pregnancy Category C

Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.

Advil 12Hour should not be used in pregnant women or women who are trying to become pregnant.

Ibuprofen inhibits prostaglandin synthesis and, when given during the latter part of a pregnancy, may cause closure of the fetal ductus arteriosus, fetal renal impairment, inhibition of platelet aggregation and may delay labour and birth.

Data from epidemiological studies suggest an increased risk of spontaneous abortion after use of prostaglandin synthesis inhibitors in early pregnancy. In animals, administration of prostaglandin synthesis inhibitors has been shown to result in increased pre- and post-implantation loss.

Reproductive studies conducted in animals did not demonstrate evidence of developmental abnormalities. However, animal reproduction studies are not always predictive of human response. There are no adequate and well-controlled studies in pregnant women.

Use in lactation.

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

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No data available.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The following adverse effects may be associated with the use of ibuprofen and are listed under their corresponding body system organ class:

- **Blood and lymphatic system disorders:** Agranulocytosis, anaemia, aplastic anaemia, haemolytic anaemia, leukopenia, thrombocytopenia.
- **Investigations:** Haematocrit decreased, haemoglobin decreased.
- **Eye disorders:** Visual disturbance.
- **Gastrointestinal disorders:** Dyspepsia, heartburn, nausea, loss of appetite, abdominal pain, abdominal pain upper, vomiting, haematemesis, abdominal distension, diarrhoea, Crohn's disease, colitis, constipation, flatulence, gastritis, gastrointestinal haemorrhage, gastrointestinal perforation, gastrointestinal ulcer, melena, mouth ulceration.
- **Nervous system disorders:** Dizziness, fatigue, headache, cerebrovascular accident.
- **Psychiatric disorders:** Nervousness.
- **Immune system disorders:** Hypersensitivity, anaphylactic reaction. Allergic reactions such as skin rash, itching, swelling of the face or breathing difficulties may occur, and these are usually transient and reversible on cessation of treatment.
- **Cardiac disorders:** Cardiac failure, myocardial infarction, angina pectoris. Fluid retention and in some cases oedema, these effects are rare at non-prescription doses.
- **Vascular disorders:** Hypertension.
- **Ear and labyrinth disorders:** Tinnitus, vertigo.
- **Hepatobiliary disorders:** Liver disorder, hepatic function abnormal, hepatitis, jaundice.
- **Infections and infestations:** Meningitis aseptic, meningitis.
- **Renal and urinary disorders:** Haematuria, interstitial nephritis, renal failure, nephrotic syndrome, proteinuria, renal papillary necrosis.
- **Respiratory, thoracic and mediastinal disorders:** Asthma, bronchospasm, dyspnoea, wheezing.
- **Skin and subcutaneous tissue disorders:** Angioneurotic oedema, dermatitis bullous, erythema multiforme, face oedema, rash, rash maculopapular, pruritus, purpura, Stevens-Johnson syndrome, urticaria. Rarely exfoliative dermatitis and toxic epidermal necrolysis have been reported with ibuprofen. Rare cases of photosensitivity.

- **General disorders and administration site conditions:** Oedema, swelling, peripheral oedema.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

The following signs and symptoms may be associated with ibuprofen overdose:

Ear and labyrinth disorders: Vertigo

Gastrointestinal disorders: Nausea, abdominal pain, vomiting

Hepatobiliary disorders: Hepatic function abnormal

Metabolism and nutrition disorders: Hyperkalaemia, metabolic acidosis

Nervous system disorders: Dizziness, somnolence, headache, loss of consciousness, convulsion

Renal and urinary disorders: Renal failure

Respiratory, thoracic and mediastinal disorders: Dyspnoea, respiratory depression

Vascular disorders: Hypotension

In case of overdose, immediately contact the Poisons Information Centre (in Australia, call 13 11 26; in New Zealand,call 0800 764 766) for advice.

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Ibuprofen possesses analgesic, antipyretic and anti-inflammatory properties, similar to other non-steroidal anti-inflammatory drugs (NSAIDs). Its mechanism of action is unknown, but is

thought to be through peripheral inhibition of cyclooxygenases and subsequent prostaglandin synthetase inhibition.

Clinical trials

Clinical efficacy studies show that Advil 12Hour provides rapid onset of analgesia which is maintained for at least 12 hours after dosing in a model of dental pain, and that this efficacy is sustained over multiple doses.

The 2 studies, AK-09-07 (single dose) and AK-10-13 (multiple dose), providing efficacy information for Advil 12Hour were conducted using the post-surgical dental pain model. In this model, patients are recruited to receive study drug following surgical extraction of impacted third molars. In Study AK-10-13, subjects were to have had removal of at least 2 third molars, and in Study AK-09-07, subjects were to have had removal of 1 or 2 third molars. In both studies, at least 1 of the extracted molars was to have been a partial or full bony mandibular impaction.

The post-surgical dental pain model is widely used in post-operative analgesia studies. Results obtained with this model have been shown to compare favourably with those from other pain models (such as general surgery, obstetrics-gynecology surgery, and bunionectomy), and hence support the applicability of results using the post-surgical dental pain model across other pain states. The intensity of pain following dental surgery (third molar extraction) is consistent and well characterised, giving the model proven sensitivity for distinguishing analgesic efficacy over this time interval. In addition, the pain lasts for several days and, although limited, the available data from multiple-dose dental pain studies suggest that the model is adequately sensitive to separate active treatments from placebo on the second post-surgical day. These characteristics make the dental pain model suitable to evaluate both single and multiple-dose efficacy (up to 48 hours) of Advil 12Hour compared with placebo.

The efficacy results of studies AK-09-07 and AK-10-13 were consistent and the combined dataset showed a significantly favorable treatment benefit for Advil 12Hour compared with placebo for all of the efficacy endpoints analysed ($p \leq 0.05$).

The individual study and combined data showed that Advil 12Hour provided significantly better efficacy compared to placebo throughout a 12-hour dosing interval, with higher mean Sum of Pain Relief and Pain Intensity Difference Scores (SPRID) at all time points (0-12, 0-4, 4-8 and 8-12 hours) and a smaller proportion of subjects using rescue medication by 4, 8 and 12 hours ($p \leq 0.05$).

The median time to first use of rescue medication (i.e. duration of relief) was significantly longer ($p \leq 0.05$) for the Advil 12Hour treatment group (>12 hours) compared with the placebo group (<2 hours).

The median times to onset of First Perceptible Relief Confirmed by Meaningful Relief (FPRC) and Meaningful Relief (MR) were significantly shorter ($p \leq 0.05$) for the Advil 12Hour treatment group (approximately 0.5 hours and 1.0 hour respectively) compared with the placebo group (>6 hours for both endpoints).

Pooled data up to 12 hours from the 2 efficacy studies demonstrate that significant analgesic efficacy of Advil 12Hour was achieved compared to placebo, for all endpoints analysed, at all-time points through 12 hours following the first dose, and in all subgroups analysed. The key end points are shown in the table below.

Key Endpoints in Studies AK-09-07 and AK-10-13 Combined (ITT Subjects)

	Advil 12Hour(N=163)	**Placebo (N=81)**			
Endpoint	**Adjusted mean (SE)**	**Adjusted mean (SE)**	**d**	**p-value**	**95% CI (d)**
SPRID 0-12 hours	47.01 (1.78)	9.78 (2.43)	37.23	<0.001*	31.28, 43.18
Endpoint	**Weighted mean (SE)**	**Weighted mean (SE)**	**d**	**p-value**	**95% CI (d)**
Proportion requiring RM by 12 hours	0.24 (0.04)	0.80 (0.04)	-0.56	<0.001*	-0.67, -0.44
Endpoint	**Median time (hours)**	**Median time (hours)**	**HR**	**p-value**	**95% CI**
Time to RM	>12	1.67	0.143	<0.001*	0.09, 0.22
Time to FPRC	0.48	>6	6.82	<0.001*	4.20, 11.06
Time to MR	1.02	>6	7.99	<0.001*	4.90, 13.01

*=Statistically significant at 0.05 level.

ITT=Intent-to-treat; N=Total number of subjects; SE=Standard Error; d= Treatment difference based on adjusted/weighted means; CI=Confidence Interval; HR=Hazard Ratio; SPRID= Sum of Pain Relief and Pain Intensity Difference Scores; RM=Rescue Medication; FPRC=First Perceptible Relief Confirmed by Meaningful Relief; MR=Meaningful Relief.

Taken together with the pharmacokinetic data demonstrating the bioequivalence of Advil 12Hour to 3 x 200 mg ibuprofen immediate release tablets, these efficacy data support the dosing recommendation of one Advil 12Hour tablet every 12 hours (with a maximum daily dose of two tablets or 1200 mg) for the relief of pain lasting for more than 6 hours.

5.2 PHARMACOKINETIC PROPERTIES

Ibuprofen is well absorbed from the gastrointestinal tract. It is highly bound (90-99%) to plasma proteins and is extensively metabolised to inactive compounds in the liver, mainly by glucuronidation. Both the inactive metabolites and a small amount of unchanged ibuprofen are excreted rapidly and completely by the kidney, with 95% of the administered dose eliminated in the urine within four hours of ingestion. The elimination half-life of ibuprofen is in the range of 1.9 to 2.2 hours.

Pharmacokinetic (PK) study (AK-10-10) was conducted to determine the rate and extent of absorption of ibuprofen in normal healthy subjects from a single dose of Advil 12Hour administered under fasted conditions compared to 3 single doses of ibuprofen 200 mg immediate release (IR) tablets (administered every 4 hours; first dose in the fasted state). This study also evaluated the PK profile of Advil 12Hour in the fed state (following a high fat meal). The PK results obtained demonstrate that the rate (C_{max}) and overall extent (AUC) of absorption of ibuprofen from Advil 12Hour in the fasted state were bioequivalent to ibuprofen 200 mg IR tablets administered every 4 hours. The results also indicated that the overall extent (AUC) of ibuprofen absorption from the Advil 12Hour was bioequivalent in the fed and fasted state, but the rate of absorption (C_{max}) was slower in the presence of food.

Pharmacokinetic study (AK-10-12) was a multiple dose PK study conducted in normal healthy subjects to compare the PK profile of Advil 12Hour versus ibuprofen 200 mg immediate release tablets at steady state, i.e., after 4 days of dosing. The results of this study demonstrate that the rate and extent of ibuprofen absorption from Advil 12Hour is bioequivalent to ibuprofen 200 mg immediate tablets after multiple doses of both formulations, i.e., there is no drug accumulation with multiple doses of Advil 12Hour.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available.

Carcinogenicity

No data available.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Advil 12Hour also contains the following inactive ingredients:

Carnauba wax, colloidal anhydrous silica, maize starch, croscarmellose sodium, hypromellose, microcrystalline cellulose, polydextrose, macrogol 400, pregelatinised maize starch, sodium lauryl sulfate, stearic acid, titanium dioxide, pharmaceutical ink (Opacode WB Blue NS-78-10521).

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.
Keep out of reach of children.

6.5 NATURE AND CONTENTS OF CONTAINER

Advil 12Hour tablets are packaged in a unit dose blister system.

Pack sizes

1 tablet (professional sample)
8 tablets
12 tablets
14 tablets
16 tablets
24 tablets
25 tablets
28 tablets
32 tablets

Not all presentations may be marketed.

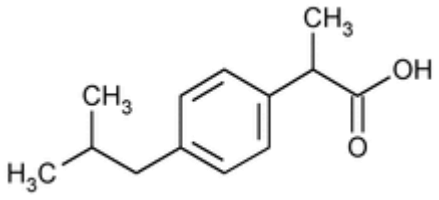
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

Ibuprofen is chemically known as *(2RS)*-2-[4-(2-Methylpropyl) phenyl] propanoic acid and has the following structure:



Ibuprofen is a white or almost white, crystalline powder or colourless crystals.

CAS number: 15687-27-1

7. MEDICINE SCHEDULE (POISONS STANDARD)

Pharmacist Only Medicine (Schedule 3)

8. SPONSOR

GlaxoSmithKline Consumer Healthcare Australia
82 Hughes Avenue Ermington NSW 2115
Telephone: 1800 028 533 Website: www.gsk.com.au

9. DATE OF FIRST APPROVAL

03 July 2018

10. DATE OF REVISION

28 August 2020

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All sections	New format
2	Addition of TGO92 allergen declarations as represented on product artwork
4	Removal of Molecular Formula and Molecular weight information
6.5	Inclusion of the nature of container as described in the submitted 'Module 3.2.P.7 – Container Closure System'
8	Change in Sponsor Name and Address details