SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Anadin Ultra

Anadin LiquiFast 200mg Capsules

Anadin Period Pain Relief 200mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Ibuprofen 200mg.

For excipients see 6.1.

3 PHARMACEUTICAL FORM

Liquid filled soft capsules.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

GSL only:
For the relief of mild to moderate pain including rheumatic and muscular pain, backache, headache, dental pain, migraine, neuralgia, dysmenorrhoea, feverishness and for the relief of symptoms of cold 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).

Adults, the elderly, and children and adolescents over 12 years of age:

If in children and adolescents, between the age of 12 and 18 years, this medicinal product is required for more than 3 days, or if symptoms worsen, a doctor should be consulted.

For adults aged 18 years or older the minimum effective dose should be used for the shortest time necessary to relieve symptoms. The patient should consult a pharmacist or a doctor if symptoms persist or worsen, or if the product is required for more than 10 days.

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

The lowest effective dose should be used for the shortest duration necessary to relieve the symptoms (see section 4.4).

The capsules should be taken with water.

Not to be used for children under 12 years of age

4.3 Contraindications

Hypersensitivity to ibuprofen or any of the constituents in this product (see Section 4.4 Special Warnings and Precautions.

Ibuprofen is contraindicated in patients who have previously shown hypersensitivity reactions (e.g. asthma, rhinitis, angiodema or urticaria) in response to aspirin or other non-steroidal anti-inflammatory drugs.

Active or previous peptic ulcer (two or more distinct episodes of proven ulceration or bleeding).

History of upper gastrointestinal bleeding or perforation, related to previous NSAID therapy.

Patients with severe hepatic failure, renal failure or severe heart failure (NYHA Class IV) (See section 4.4).

Use in last trimester of pregnancy (See section 4.6 Fertility, Pregnancy and Lactation).

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 prior to starting treatment in patients with a history of hypertension and/or heart failure. Oedema, hypertension and/or cardiac impairment as renal function may deteriorate and/or fluid retention occur (see Section 4.8)
- Renal impairment as renal function may deteriorate (see Section 4.3 and 4.8)
- Hepatic dysfunction (see 4.3 and 4.8)

Undesirable effects may be minimised by using the minimum effective dose for the shortest possible duration necessary to control symptoms. (See GI and cardiovascular risks below).

Renal tubular acidosis and hypokalaemia may occur following acute overdose and in patients taking ibuprofen products over long periods at high doses (typically greater than 4 weeks), including doses exceeding the recommended daily dose.

The elderly are at increased risk of the serious consequences of adverse reactions.

Caution should be exercised when initiating treatment with ibuprofen in children with considerable dehydration. There is a risk of renal impairment in dehydrated children.

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

Use with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided (see section 4.5).

Cardiovascular and cerebrovascular effects

Clinical studies suggest that use of ibuprofen, particularly at high doses (2400 mg/day) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke). Overall, epidemiological studies do not suggest that low dose ibuprofen (e.g. $\leq$ 1200 mg 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.

Cases of Kounis syndrome have been reported in patients treated with Anadin Joint Pain. Kounis syndrome has been defined as cardiovascular symptoms secondary to an allergic or hypersensitive reaction associated with constriction of coronary arteries and potentially leading to myocardial infarction.

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 upon withdrawal of treatment.

GI bleeding, ulceration and perforation, which can be fatal, has been reported with all NSAIDs at any time during treatment, with or without warning symptoms or a previous history of serious GI events (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 gastrotoxicity or bleeding, such as corticosteroids, or anticoagulants such as warfarin, selective serotonin re-uptake inhibitors 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.

Severe cutaneous adverse reactions (SCARs): Severe cutaneous adverse reactions (SCARs), including exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome (SJS), Toxic Epidermal Necrolysis (TEN), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS syndrome), and acute generalized exanthematous pustulosis (AGEP), which can be life-threatening or fatal, have been reported in association with the use of ibuprofen (see section 4.8). Most of these reactions occurred within the first month.

If signs and symptoms suggestive of these reactions appear Anadin Joint Pain should be withdrawn immediately and an alternative treatment considered (as appropriate).

<u>Masking of symptoms of underlying infections</u>
Anadin Ultra can mask symptoms of infection, which may lead to delayed initiation of appropriate treatment and thereby worsening the outcome of the infection. This has

been observed in bacterial community acquired pneumonia and bacterial complications to varicella. When Anadin Ultra is administered for fever or pain relief in relation to infection, monitoring of infection is advised. In non-hospital settings, the patient should consult a doctor if symptoms persist or worsen.
Patients with rare hereditary problems of fructose intolerance should not take this medicine. This medicine contains 40mg of potassium per dose. To be taken into consideration by patients with reduced kidney function or patients on a controlled potassium diet.
There is a risk of renal impairment in dehydrated children and adolescents, between the ages of 12-18 year olds.

Keep out of sight and reach of children.

The label will include:
12-18 years: if symptoms worsen, or persist for more than 3 days, or you get new symptoms consult your doctor.
Adults: if symptoms worsen, or persist for more than 10 days, or you get new symptoms consult your pharmacist or doctor.
Read the enclosed leaflet before taking this product.

Do not take if you:
• have ever had a stomach ulcer, perforation or bleeding
• are allergic to ibuprofen (or anything else in this medicine), aspirin or other related painkillers
• are taking other NSAID painkillers, or aspirin with a daily dose above 75mg
• are in the last 3 months of pregnancy.
Speak to a pharmacist or your doctor before taking if you:
• have asthma, diabetes, high cholesterol, high blood pressure, had a stroke, heart, liver, kidney or bowel problems
• are a smoker
• are pregnant

4.5 Interaction with other medicinal products and other forms of interaction

Ibuprofen should not be used in combination with:

Acetylsalicylic acid

Concomitant administration of ibuprofen and aspirin (acetylsalicylic acid) is not generally recommended (unless low-dose aspirin (not above 75mg daily) has been advised by a doctor), as this combination may increase the risk of adverse reactions (see Section 4.4).

Experimental data suggest that ibuprofen may competitively inhibit the effect of low dose aspirin (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 aspirin (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 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 effect of these drugs. Diuretics can increase the risk of nephrotoxicity of NSAIDs.

Anticoagulants: NSAIDs may enhance the effects of anti-coagulants, such as warfarin (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 the potential for increased plasma levels of 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: 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.

4.6 Fertility, Pregnancy and lactation

Pregnancy:

From the 20th week of pregnancy onward, Anadin Ultra use may cause oligohydramnios resulting from foetal renal dysfunction. This may occur shortly after treatment initiation and is usually reversible upon discontinuation. In addition, there have been reports of ductus arteriosus constriction following treatment in the second trimester, most of which resolved after treatment cessation. Therefore, during the first and second trimester of pregnancy, Anadin Ultra should not be given unless clearly necessary. If Aandin Ultra 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. Antenatal monitoring for oligohydramnios and ductus arteriosus constriction should be considered after exposure to Anadin Ultra for several days from gestational week 20 onward. Anadin Ultra should be discontinued if oligohydramnios or ductus arteriosus constriction are found.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to:

- cardiopulmonary toxicity (with premature constriction/closure of the ductus arteriosus and pulmonary hypertension);

- renal dysfunction (see above);

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, Anadin Ultra is contraindicated during the third trimester of pregnancy (see sections 4.3 and 5.3).

Lactation:

In limited studies, ibuprofen appears in the 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

No studies on the effect of ability to drive or use machines have been performed.

4.8 Undesirable effects

Adverse reactions reported from extensive post-marketing experience are tabulated below by System Organ Class and frequency. The following convention has been utilised for the classification of undesirable effects: very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1000, <1/100), rare (≥1/10000, <1/1000), very rare (<1/10000), not known (cannot be estimated from available data).

The following list of adverse effects relates to those experienced with ibuprofen at OTC doses, for short term use. In treatment of chronic conditions, under long-term treatment, additional adverse effects may occur.

Body System	Undesirable effect	Frequency
Gastrointestinal disorders	Nausea, dyspepsia, diarrhoea, vomiting	Common
	Abdominal pain, flatulence, constipation	Uncommon
	Intestinal diaphragm disease	Rare
	Peptic ulcer, perforation or gastrointestinal haemorrhage, sometimes fatal, particularly in the elderly. Exacerbation of ulcerative colitis and Crohn's disease (*see Warnings and Precautions).*	Very rare
Psychiatric disorders	Nervousness	Rare
Nervous system disorders	Headache, drowsiness, dizziness	Common
Metabolism and Nutrition Disorders	Decreased appetite and Hypokalaemia*	Not known
Renal and urinary disorders	Tubulointerstitial nephritis, nephrotic syndrome, haematuria, proteinuria	Rare
	Acute renal failure, papillary necrosis, especially in long-term use, associated with increased serum urea and oedema.	Very rare
	Uretic colic, dysuria and renal tubular acidosis*	Not known
Hepatobiliary disorders	Liver disorders.	Very rare

Blood and lymphatic system disorders	Haematopoietic disorders (anaemia, leucopenia, thrombocytopenia, pancytopenia, agranulocytosis). First signs are: fever, sore throat, superficial mouth ulcers, flu-like symptoms, severe exhaustion, unexplained bleeding and bruising.	Very rare
Cardiac disorders	Cardiac failure *(see Warnings and Precautions)*	Rare
	Kounis Syndrome	Not known
Vascular disorders	Hypertension *(see Warnings and Precautions)*	Rare
	Arterial thrombotic events e.g. myocardial infarction or stroke	Not known
General disorders and administration site conditions	Oedema *(see Warnings and Precautions)*	Rare
Skin and subcutaneous tissue disorders	Skin rashes	Uncommon
	Severe cutaneous adverse reactions (SCARs) (including Erythema multiforme, exfoliative dermatitis, Stevens-Johnson Syndrome, and toxic epidermal necrolysis)	Very rare
	Drug reaction with eosinophilia and systemic symptoms (DRESS)	Very rare
	Photosensitivity reactions	Not known
	Acute generalized exanthematous pustulosis (AGEP)	Not known
Immune system disorders	Hypersensitivity reactions including: • Urticaria and pruritus	Uncommon
	• In patients with existing auto-immune disorders (such as systemic lupus erythematosus, mixed connective tissue disease) during treatment with ibuprofen, single cases of symptoms of aseptic meningitis, such as stiff neck, headache, nausea, vomiting, fever or disorientation have been observed (*see Warnings and Precautions*).	Rare

Immune system disorders	• Severe hypersensitivity reactions. Symptoms could be: facial, tongue and laryngeal swelling, dyspnoea, tachycardia, hypotension (anaphylaxis, angioedema or severe shock). • Exacerbation of asthma and bronchospasm.	Very rare
Eye disorder	Visual disturbances	Rare
Ear and labyrinth disorders	Tinnitus	Uncommon
	Vertigo	Rare

Description of Selected Adverse Reactions
*Renal tubular acidosis and hypokalaemia have been reported in the post-marketing setting typically following prolonged use of the ibuprofen component at higher than recommended doses.

Clinical trial and epidemiological data suggest that use of ibuprofen (particularly at high doses 2400 mg 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).

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 the Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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, hypokalaemia 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.

In serious poisoning 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.

Prolonged use at higher than recommended doses may result in severe hypokalaemia and renal tubular acidosis. Symptoms may include reduced level of consciousness and generalised weakness (see section 4.4 and section 4.8).

Management

Management should be symptomatic and supportive and include the maintenance of a clear airway and monitoring of cardiac and vital signs until stable. Consider oral administration of activated charcoal if the patient presents within 1 hour of ingestion of a potentially toxic amount. If frequent or prolonged, convulsions should be treated with intravenous diazepam or lorazepam. Give bronchodilators for asthma.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Propionic acid derivatives

ATC code: 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 liquigels are evident within around 30 minutes of dosing. The effects of a 400mg dose of ibuprofen liquigels 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. From the same studies, a single dose of 200mg did not show significant differences in onset of analgesia when compared to 1000mg paracetamol.

Clinical Parameters	**Ibuprofen Liquigels 200mg**	**Ibuprofen Liquigels 400mg**	**Acetaminophen 1g (2 x 500mg)**	**Placebo**
Packman et al				
Total Pain Relief (TOTPAR)	N/A	N/A	N/A	N/A
Sum of Pain Relief & Pain Intensity Difference (SPID)	N/A	15.2	12.2	5.8

Time to Meaningful Relief (mins)	N/A	39	53	>180
Hersch et al				
Total Pain Relief (TOTPAR)	14.72	16.56	11.99	5.25
Sum of Pain Relief & Pain Intensity Difference (SPID)	6.93	8.07	5.05	0.46
Time to Meaningful Relief (mins)	30.0	28.8	29.4	>360
Olson et al				
Total Pain Relief (TOTPAR)	N/A	17.42	13.30	4.33
Sum of Pain Relief & Pain Intensity Difference (SPID)	N/A	11.77	8.36	2.60
Time to Meaningful Relief (mins)	N/A	24.2	29.9	>360
Kellstein et al				
Total Pain Relief (TOTPAR)	36	30	N/A	52
Pain Intensity Difference (PID) after 2 hours	0.98	0.97	N/A	0.87
Time to Meaningful Relief (mins)	N/A	N/A	N/A	N/A

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

Experimental data suggest that ibuprofen may competitively inhibit the effect of low dose aspirin (acetylsalicylic acid) on platelet aggregation when they are dosed concomitantly. Some pharmacodynamic studies show that when single doses of ibuprofen 400mg were taken within 8 hours before or within 30 min after immediate release aspirin (acetylsalicylic acid) dosing (81mg), a decreased effect of aspirin (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 aspirin (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. The excretion is rapid and complete via the kidneys. 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.

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

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule Contents:

Macrogol 600

Potassium Hydroxide

Capsule Shell:

Sorbitol liquid, partially dehydrated

Gelatin

Quinoline yellow E104

Patent blue V E131

Purified water

Processing Aids:

Lecithin

Triglycerides (medium chain)

Glyceryl stearate

Oleic acid

Ascorbyl palmitate

Printing Ink:

Opacode white ink (E171, propylene glycol, polyvinyl acetate phthalate, polyethylene glycol).

6.2 Incompatibilities

None known.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Anadin Ultra/ Anadin LiquiFast 200mg Capsules/ Anadin Period Pain Relief 200mg Capsules is packed into blister strips of 4, 6, 8, 10, 12 and 16 capsules in a cardboard box.

Pack A:	PVdC (60gsm)/white opaque PVC (200μm)/heat sealed to the foil.
	Foil: Hard temper aluminium foil (20 μm)/Heatseal lacquer (7 gsm).
Pack B: Blister:	White opaque thermoformed unplasticised PVC (250 μm)/ PVdC coating (60 gsm) heat sealed to the foil.
	Foil: Glassine (35 gsm)/Lamination adhesive/Aluminium foil (9 μm)/Heatseal lacquer (7 gsm).

6.6 Special precautions for disposal

No special instructions.

7 MARKETING AUTHORISATION HOLDER

GlaxoSmithKline Consumer Healthcare (UK) Trading Limited,
Brentford,
TW8 9GS,
U.K.

8 MARKETING AUTHORISATION NUMBER(S)

PL 44673/0205

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