Public Assessment Report
Anadin Ultra Double Strength 400mg Capsules
PL 00165/0148

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</table>
Lay Summary

The MHRA granted Whitehall Laboratories a Marketing Authorisation (licence) for the medicinal product Anadin Ultra Double Strength 400mg Capsules on 11th May 2006. Anadin Ultra Double Strength 400mg Capsules has been indicated for the relief of rheumatic or muscular pain, pain of non-serious arthritic conditions, backache, neuralgia, migraine headache, dental pain, dysmenorrhoea, feverishness, symptoms of colds and influenza.

This application has been made under 2001/83/EC Article 10.1 as amended, claiming essential similarity to Brufen Tablets 400 mg, first licensed to The Boots Company plc as PL 00014/0158R in October 1981.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Anadin Ultra Double Strength 400mg Capsules outweigh the risks, hence a Marketing Authorisation has been granted.
Scientific Discussion

INTRODUCTION

This Public Assessment report is based on the assessment report for a national standard abridged application for Marketing Authorisation in the UK submitted under Directive 65/65/EEC, Art 4.8(a) (iii), for a liquid-fill soft gelatin capsule formulation containing Ibuprofen Ph Eur by Whitehall Laboratories Ltd (PL 00165/0148). The Marketing Authorisation was granted on 11/05/2006. Essential similarity was claimed to Brufen Tablets 400 mg, first licensed to The Boots Company plc as PL 00014/0158R in October 1981. PL 00014/0158R was cancelled and taken over by PL 13530/0006, granted to Knoll Pharma Ltd in April 1993, which was in turn taken over by PL 00169/0050, granted to Knoll Limited in July 1995. Cross-reference has been made to Brufen 400 mg tablets (Knoll Ltd – Austria).

Anadin Ultra Double Strength 400mg Capsules are indicated for the relief of rheumatic or muscular pain, pain of non-serious arthritic conditions, backache, neuralgia, migraine headache, dental pain, dysmenorrhoea, feverishness, symptoms of colds and influenza.

PHARMACEUTICAL ASSESSMENT

Drug Substance

A copy of the Ph Eur Certificate of Suitability for the source of Ibuprofen was provided. The proposed Drug Substance Specification complies with the Ph Eur and USP monographs for Ibuprofen and is acceptable. Satisfactory batch analyses data has been provided for the drug substance. The re-test date of 3 years is supported by satisfactory stability data when the drug substance is stored at <30°C.

Finished Product

The proposed product was presented as a size 14 oval capsule with a dye-free, translucent gelatin shell containing 400 mg of Ibuprofen as a clear liquid fill. The soft capsules are packed in two types of thermoformed PVC/PE/PVdC/aluminium blisters and inserted into a folded cardboard box. The liquor fill capsules contain the same active ingredient at the same concentration as the claimed essentially similar preparation, PL 00169/0050 - Brufen Tablets 400 mg.

The qualitative formulation for the finished product is ibuprofen, Polyethylene Glycol 600, Potassium Hydroxide 50% Solution (in purified water), Anidrisorb 85/70, Gelatin (150 bloom), Purified water, and Opacode NSP-78-17734 (Black). The following are also used as processing aids but not found in the finished product; Ribbon printing solvent (ink thinner), Ethanol BP, Water for irrigation. The level of each excipient in the formulation is similar to other products marketed in the UK. Evidence of compliance
with the corresponding Ph Eur. Monographs have been provided for excipients. TSE certificates have been provided for all sources of gelatine.

The dosage form is a soft liquid-gel formulation providing faster absorption of the single active ingredient, Ibuprofen, than comparable tablet dosage forms. The translucent softgel is claimed to be aesthetically pleasing and a dye-free oval shape has been selected due to its preferable marketing appearance.

The proposed manufacturing process has been adequately summarised and a satisfactory flow diagram presented. The manufacturing process involves encapsulating a liquid fill inside a soft gelatin shell. A satisfactory finished product specification was provided with an appropriate description of analytical methods and satisfactory batch analyses data. Stability data supporting the shelf-life of 24 months stored below 30°C has been provided.

**CLINICAL ASSESSMENT**

**INDICATIONS**

The indications for Anadin Ultra Double Strength 400mg Capsules, as for Brufen 400mg, are 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 flu. It may also be used for relief of the pain of non-serious arthritic conditions.

For all indications, the dose for adults, the elderly and adolescents over 12 years of age is 1 capsule taken up to three times daily (maximum 1200mg in 24 hours), with water. The capsules are not suitable for children under 12 years of age.

**TOXICOLOGY**

No formal data are presented and none are required for this application. The toxicological and pharmacological profile of ibuprofen is well known and understood.

**CLINICAL PHARMACOLOGY**

As the clinical expert avers, the pharmacodynamics and pharmacokinetics of ibuprofen are well known and have been for some considerable time.

**BIOEQUIVALENCE**

Bioequivalence was investigated in a single dose, randomised open label, four way, crossover study in 24 health male subjects, Protocol 068-60. This was a study to assess the single dose pharmacokinetics of a 400mg dose of ibuprofen administered as 1 x 400mg Advil® Liqui-Gel
(European, HA/100/1065), 1 x Anadin Ultra 400 (European, HA/100/1066), 2 x 200mg Advil® Liqui-Gel (US), and 1 x 400mg Brufen® Tablet (Knoll Ltd) – Protocol 068-60.

The primary objective was to compare the rate and extent of ibuprofen absorption from Anadin Ultra Double Strength 400mg Capsules (product code HA/100/1066 – treatment B) with the 400mg Brufen tablet (Knoll Ltd, UK, treatment D) under fasting conditions. The rate and extent of ibuprofen absorption from the two Advil products were also investigated.

7ml blood samples were collected during each study period at time 0 and at 10, 20, 30, 40, 50, 60, 75 and 90 minutes and 2, 3, 4, 6, 8, 10, 12 and 16 hours post dose, and the plasma concentrations of racemic ibuprofen were determined following each single dose administration.

Pharmacokinetic parameters $C_{\text{max}}$, $T_{\text{max}}$, $\text{AUC}(0-t)$, $\text{AUC}(0-\infty)$ were calculated. The 90% confidence intervals were calculated for straight and log (In)-transformed $C_{\text{max}}$, $\text{AUC}(0-t)$ and $\text{AUC}(0-\infty)$.

Although 24 male subjects were enrolled, only 22 completed the trial and one of these was excluded from the statistical analysis due to missing plasma samples.

The results and statistical comparisons for the Anadin Ultra 400 and Brufen tablet are shown in the following table.

**Summary of the Pharmacokinetic Parameters of Plasma Ibuprofen for Treatments B and D**

<table>
<thead>
<tr>
<th>Plasma Ibuprofen</th>
<th>Treatment B</th>
<th>Treatment D</th>
<th>90% CI*</th>
<th>% Mean Ratio *</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (ug/mL)</td>
<td>47.1499 8.6686</td>
<td>35.1237 12.1755</td>
<td>122.3 – 144.4</td>
<td>133.3</td>
</tr>
<tr>
<td>$T_{\text{max}}$ (hr)</td>
<td>0.618 0.147</td>
<td>1.66 1.15</td>
<td>17.0 – 56.6</td>
<td>36.8</td>
</tr>
<tr>
<td>AUC (0-t) (ug*hr/mL)</td>
<td>113.7 23.43</td>
<td>112.5 27.47</td>
<td>96.8 – 105.1</td>
<td>100.9</td>
</tr>
<tr>
<td>AUC (0-\infty) (ug*hr/mL)</td>
<td>114.9 23.71</td>
<td>113.9 27.41</td>
<td>96.7 – 104.9</td>
<td>100.8</td>
</tr>
<tr>
<td>$t_{\frac{1}{2}}$ (hr)</td>
<td>1.88 0.242</td>
<td>1.97 0.293</td>
<td>90.8 – 101.9</td>
<td>96.4</td>
</tr>
<tr>
<td>$K_{\text{el}}$ (1/hr)</td>
<td>0.374 0.0487</td>
<td>0.0358 0.0517</td>
<td>98.1 – 108.6</td>
<td>103.4</td>
</tr>
<tr>
<td>LN ($C_{\text{max}}$)</td>
<td>3.838 0.1819</td>
<td>3.500 0.3556</td>
<td>125.4 – 153.6</td>
<td>138.8</td>
</tr>
<tr>
<td>LN[AUC(0-t)]</td>
<td>4.713 0.2059</td>
<td>4.694 0.2433</td>
<td>97.2 – 106.1</td>
<td>101.5</td>
</tr>
<tr>
<td>LN[AUC(0-\infty)]</td>
<td>4.724 0.2060</td>
<td>4.708 0.2398</td>
<td>97.1 – 105.8</td>
<td>101.3</td>
</tr>
</tbody>
</table>

As can be seen from these results, Anadin Ultra 400 and the 400mg tablet of Brufen from Knoll Ltd are bioequivalent with respect to AUC since the 90% confidence intervals for the least squares means parameter values are within 80% to 125% for both straight and In-transformed $\text{AUC}(0-t)$ and $\text{AUC}(0-\infty)$.

So far as $C_{\text{max}}$ was concerned, however, bioequivalence criteria were not met, the level being 33% higher for Anadin Ultra 400, with $T_{\text{max}}$ being approximately 1 hour earlier.
Thus, while bioequivalence has been confirmed, there is also evidence of a faster rate of absorption to a higher peak, though total absorption is bioequivalent. This is delineated in section 5.2 Pharmacokinetic Properties of the SPC, as is the half-life of just under 2 hours, very much the same as for Brufen 400mg tablet.
EFFICACY

No new efficacy data are presented in this application and none are required.

SAFETY

No formal safety data are presented and none are required.

EXPERT REPORT

There is an adequate expert report by a suitably qualified expert.

SUMMARY OF PRODUCT CHARACTERISTICS

The Summary of Product Characteristics was amended and can be found on page 10 of this report.

PATIENT INFORMATION LEAFLET

The Patient Information Leaflet was updated in line with changes made to the SPC.

LABELLING

The labelling is satisfactory.

DISCUSSION

This standard application for 400 mg tablets of ibuprofen under the trade name of Anadin Ultra Double Strength 400 mg Capsules is satisfactory. The company have shown bioequivalence to the brand leader Brufen 400mg tablets, though with a more rapid onset of action. No unexpected adverse events were found during the trial. A Marketing Authorisation was granted.
Overall Conclusion and Risk/Benefit Analysis

**Quality**
The quality aspects of Anadin Ultra Double Strength 400mg Capsules are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

**Pre-Clinical**
No new pre-clinical data were presented or were required for this type of application.

**Clinical**
Bioequivalence has been established although with evidence of a faster rate of absorption to a higher peak. Total absorption is bioequivalent and there are no clinical issues that would have negative impact on the risk/benefit balance.

**Risk/Benefit Analysis**
The quality of the product is acceptable and the product is essentially similar to the reference product the product has a positive risk/benefit assessment. A Marketing Authorisation was granted.
Steps Taken During Assessment

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<table>
<thead>
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<tbody>
<tr>
<td>1</td>
<td>The MHRA received the application on 19(^{th}) September 2000.</td>
</tr>
<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the applications valid on 6(^{th}) October 2000.</td>
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<tr>
<td>3</td>
<td>Following assessment of the applications the MHRA requested further information relating to the quality dossier on 14(^{th}) December 2000, 24(^{th}) February 2004, and further information relating to the clinical dossier on 21(^{st}) August 2001, 24(^{th}) February 2004</td>
</tr>
<tr>
<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information on the quality dossier on the 12(^{th}) July 2001, 27(^{th}) October 2004 and further information on the clinical dossier was supplied on 2(^{nd}) February 2004, 27(^{th}) October 2004 and 11(^{th}) November 2004.</td>
</tr>
<tr>
<td>5</td>
<td>The application was determined on 11(^{th}) May 2006.</td>
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</table>
SUMMARY OF PRODUCT CHARACTERISTICS

1. Trade Name of the Medicinal Product
   Anadin Ultra Double Strength 400 mg Capsules

2. Qualitative and Quantitative Composition
   Each capsule contains 400mg Ibuprofen
   For excipients, see 6.1

3. Pharmaceutical Form
   Soft capsule
   A 14 oval capsule with a dye free, translucent gelatin shell, printed with ‘400’ in black ink, and containing a clear liquid fill.

Clinical Particulars

4.1. Therapeutic Indications
   For relief of rheumatic or muscular pain, pain of non-serious arthritic conditions, backache, neuralgia, migraine, headache, dental pain, dysmenorrhea, feverishness, symptoms of colds and influenza.

4.2. Posology and Method of Administration
   For oral administration and short term use only.

   Adults, the elderly and young persons over 12 years of age:
   The minimum effective dose should be used for the shortest time necessary to relieve symptoms. If the product is required for more than 10 days or if the symptoms worsen, the patient should consult a doctor.
   1 capsule up to 3 times a day, as required.
   The capsules should be taken with water.
   Leave at least 4 hours between doses and do not take more than 1200 mg (3 capsules) in any 24 hour period.
   Not to be used for children under 12 years of age.

4.3. Contra-indications
Hypersensitivity to ibuprofen or any of the constituents in the product.
Ibuprofen is contraindicated in patients who have previously shown hypersensitivity reactions (e.g. asthma, rhinitis, or urticaria) in response to aspirin or other non steroidal anti-inflammatory drugs.
Active or previous peptic ulcer.
History of upper gastrointestinal bleeding or perforation, related to previous NSAID therapy.
Patients with severe hepatic failure, severe renal failure or severe heart failure. (See section 4.4).
Use with concomitant NSAIDs including cyclo-oxygenase-2 specific inhibitors (See section 4.5).
Use in third trimester of pregnancy.

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).
- hypertension and/or cardiac impairment as renal function may deteriorate and/or fluid retention occur (see section 4.5).
- renal impairment as renal function may deteriorate (see section 4.3 and 4.8).
- hepatic dysfunction (see section 4.3 and 4.8).

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

Undesirable effects may be minimised by using the minimum effective dose for the shortest possible duration.

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

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

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.

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

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 gastrointestinal bleeding, such as corticosteroids, or anticoagulants such as warfarin or anti-platelet agents such as aspirin (see section 4.5).

Patients with rare hereditary problems of fructose intolerance should not take this medicine.

4.5. Interactions with other Medicaments and other forms of Interaction
Ibuprofen should not be used in combination with:

Aspirin: unless low dose aspirin (not above 75mg daily) has been advised by a doctor, as this may increase the risk of adverse reactions (see section 4.3). Other NSAIDs: as these may increase the risk of adverse effects (see section 4.3).

Ibuprofen should be used with caution in combination with:

Corticosteroids: may increase the risk of adverse reactions, especially of the gastrointestinal tract (see section 4.4). Antihypertensives and diuretics: NSAIDs may diminish the effects of these drugs. Anticoagulants: NSAIDs may enhance the effects of anticoagulants, such as warfarin (see section 4.4). Lithium: There is evidence for potential increase in plasma levels of lithium. Methotrexate: There is the potential for increased plasma levels of methotrexate. Zidovudine: There is evidence of an increased risk of haemarthroses and haematoma in HIV positive haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.

4.6. Pregnancy and Lactation

Pregnancy

While no teratogenic effect has been demonstrated in animal experiments, use of Ibuprofen should 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 duration of labour increased, with increased bleeding tendency in both mother and child (see section 4.3).

Lactation

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

See section 4.4 regarding female fertility.

4.7. Effects on Ability to Drive and Use Machines

None.

4.8. Undesirable Effects

Hypersensitivity reactions have been reported and these may consist of:

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

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

<table>
<thead>
<tr>
<th>Infections and infestations</th>
<th>Very rare: Aseptic meningitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disorder</td>
<td>Frequency</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Blood and lymphatic disorders</td>
<td>Very rare</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Very rare</td>
</tr>
<tr>
<td></td>
<td>Very rare</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Very rare</td>
</tr>
<tr>
<td>Nervous System</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Very rare</td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td>Very rare</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Very rare</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Very rare</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Very rare</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
</tr>
<tr>
<td></td>
<td>Very rare</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>Very rare</td>
</tr>
</tbody>
</table>

UKPAR Anadin Ultra 400, Whitehall Laboratories
Skin and subcutaneous tissue disorders

Uncommon: Various skin rashes

Very rare: Severe forms of skin reactions such as erythema multiforme and epidermal necrolysis can occur.

Renal and urinary disorders

Very rare: Acute renal failure, papillary necrosis, especially in long-term use, associated with increased serum urea and oedema.

General disorders and administration site conditions

Very rare: Oedema, peripheral oedema

Investigations

Very rare: Decreased hematocrit and hemoglobin levels

4.9. Overdose

In children ingestion of more than 400mg/kg may cause symptoms. In adults the dose response effect is less clear cut. The half-life in overdose is 1.5-3 hours.

Symptoms – Most patients who have ingested clinically important amounts of NSAIDs will develop no more than nausea, vomiting, epigastric pain, or more rarely diarrhoea. Tinnitus, headache and gastrointestinal bleeding are also possible. In more serious poisoning, toxicity is seen in the central nervous system, manifesting as vertigo, headache, respiratory depression, dyspnoea, drowsiness, occasionally excitation and disorientation or coma. Occasionally patients develop convulsions. In serious poisoning, hypotension, hyperkalaemia, and metabolic acidosis may occur and the prothrombin time / INR may be prolonged, probably due to interference with the actions of circulating clotting factors. Acute renal failure and liver damage may occur. Exacerbation of asthma is possible in asthmatics.

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

5.0 Pharmacological Properties

5.1. Pharmacodynamic Properties

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.

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. Maximum plasma concentrations are reached in 45 minutes after ingestion if taken on an empty stomach. When taken with food, peak levels are observed after 1 to 2 hours. These
times may vary with different dosage forms.

The half-life of ibuprofen is about 2 hours.

In limited studies, ibuprofen appears in the breast milk in very low concentrations.

5.3. **Preclinical Safety Data**

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

**Pharmaceutical Particulars**

6.1. **List of Excipients**

**Capsule Contents:**
Macrogol 600
Potassium hydroxide

**Capsule shell:**
Sorbitol liquid, partially dehydrated (containing sorbitan and mannitol)
Gelatin
Purified water

**Processing Aids:**
Lecithin
Triglycerides (medium chain)

**Printing Ink:**
Opacode black ink [iron oxide black (E172), propylene glycol, polyvinyl acetate phthalate (PVAP), macrogol 400].

6.2. **Incompatibilities**

None known.

6.3. **Shelf Life**

24 months

6.4. **Special Precautions for Storage**

Do not store above 30°C.
6.5. **Nature and Contents of Container**

Anadin Ultra Double Strength 400 mg capsules are packed into blister strips in a cardboard box. White, opaque PVC/PE/PVdC coating and hard aluminium foil.

Pack sizes of 10 and 20 capsules.

6.6. **Instruction for Use/Handling**

No special instructions.

7. **Marketing Authorisation Holder**

Whitehall Laboratories Ltd trading as Wyeth Consumer Healthcare
Huntercombe Lane South
Taplow
Maidenhead
Berkshire
SL6 0PH
United Kingdom

8. **Marketing Authorisation Number**

PL 00165/0148

9. **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

11/05/2006

10. **DATE OF REVISION OF THE TEXT**

11/05/2006