SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Lodine 600 mg SR Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 600 mg of etodolac.

Excipients with known effect
Each tablet contains 109 mg lactose and 34 mg of sodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Lodine SR Tablets are for oral administration. Each tablet is capsular, oval shaped light grey film coated, impressed on one side with Lodine SR600 and contains etodolac 600mg in a sustained release formulation.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Lodine (etodolac) is indicated for acute or long-term use in rheumatoid arthritis and osteoarthritis.

4.2 Posology and method of administration

Posology

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

Adults: One tablet daily. If a lower dose is sufficient, conventional Lodine capsules or tablets may be used.
The safety of doses in excess of 600mg per day has not been established.

No occurrence of tolerance or tachyphylaxis has been reported.

Elderly: No change in initial dosage is generally required in the elderly (see precautions). The elderly are at increased risk of the serious consequences of adverse reactions. If an NSAID is considered necessary, the lowest effective dose should be used and for the shortest

possible duration. The patient should be monitored regularly for GI bleeding during NSAID therapy.

Paediatric population: Not recommended.

Method of administration

For oral administration.

To be taken preferably with or after food. Swallow the tablet whole with a tumblerful of water.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Lodine should not be used in patients with severe heart failure.

Lodine should not be used in patients with active or history of recurrent peptic ulceration or a history of peptic ulcer disease (with two or more distinct episodes of proven ulceration or bleeding).

NSAIDs are contraindicated in patients who have previously shown hypersensitivity reactions (e.g. asthma, rhinitis angioedema or urticaria) during therapy with ibuprofen, aspirin or other non-steroidal anti-inflammatory drugs.

Severe heart failure, hepatic failure and renal failure (see section 4.4)

During the last trimester of pregnancy (see section 4.6)

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

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 section 4.2, and GI and cardiovascular risks below).

The use of Lodine with concomitant NSAIDs including cyclooxygenase-2-selective inhibitors should be avoided (see section 4.5)

Elderly:
The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal (see section 4.2)

Cardiovascular and cerebrovascular effects:
Appropriate monitoring and advice are required for patients with a history of hypertension and/or mild to moderate congestive heart failure as fluid retention and oedema have been reported in association with NSAID therapy.

Clinical trial and epidemiological data suggest that use of some NSAIDs (particularly at high doses and in long term treatment) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke). There are insufficient data to exclude such a risk for Lodine.

Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with Lodine after careful consideration. Similar consideration should be made before initiating longer-term treatment of patients with risk factors for cardiovascular disease (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking).

Respiratory disorders:
Caution is required if Lodine is administered to patients suffering from, or with a previous history of, bronchial asthma since NSAIDs have been reported to precipitate bronchospasm in such patients.

Cardiovascular, Renal and Hepatic Impairment:
In patients with renal, cardiac or hepatic impairment especially those taking diuretics and the elderly, renal function should be monitored in these patients (see also section 4.3). Caution is required since the use of NSAIDs may result in a dose dependent reduction in prostaglandin formation and precipitate renal failure. The dose should be kept as low as possible. However, impairment of renal or hepatic functions due to other causes may alter drug metabolism; patients receiving concomitant long term therapy, especially the elderly, should be observed for potential side effects and their drug doses adjusted as needed, or the drug discontinued.

Gastrointestinal bleeding, ulceration and perforation:
Serious gastrointestinal adverse effects such as bleeding, ulceration and perforation, which can be fatal, has been reported and can occur at any time with or without warning symptoms in patients treated with NSAIDs or a previous history of serious GI events. If any sign of gastrointestinal bleeding occurs, Lodine should be stopped immediately.

Platelets:
Although non-steroidal anti-inflammatory drugs do not have the same direct effects on platelets as does aspirin, all drugs which inhibit the biosynthesis of prostaglandins may interfere, to some extent, with platelet function. Patients receiving Lodine who may be adversely affected by such actions should be carefully observed.
Patients on long-term treatment with Lodine should be regularly reviewed as a precautionary measure e.g. for changes in, renal function, haematological parameters, or hepatic function.

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 . Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low dose aspirin, or other drugs likely to increase gastrointestinal risk (see below and section 4.5)

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 oral corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors or anti-platelet agents such as aspirin (see section 4.5).

When GI bleeding or ulceration occurs in patients receiving Etodolac, the treatment should be withdrawn.

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)

SLE and mixed connective tissue disease:
In patients with systemic lupus erythematous (SLE) and mixed connective tissue disorders there may be an increased risk of aseptic meningitis (see section 4.8).

Dermatological
Severe cutaneous adverse reactions (SCARs):
Serious skin reactions including such as exfoliative dermatitis, Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and acute generalised exanthematous pustulosis (AGEP), which can be life-threatening or fatal, have been reported very rarely in association with the use of NSAIDs and etodolac treatment (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. Lodine should be discontinued at the first appearance of the skin rash, mucosal lesions, or any other sign of hypersensitivity.
Patients should be advised of the signs and symptoms of the severe cutaneous adverse reactions and should seek medical advice from their physician immediately when observing any indicative signs or symptoms. If signs and symptoms suggestive of these reactions appear, etodolac should be withdrawn immediately and an alternative treatment considered (as appropriate).

If the patient has developed a severe cutaneous adverse reaction such as SJS, TEN or AGEP with the use of etodolac, treatment with etodolac must not be restarted in this patient at any time.

Lactose
Lodine contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Sodium
This medicinal product contains 34 mg of sodium per tablet, equivalent to 1.7% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

Since Lodine is extensively protein-bound, it may be necessary to modify the dosage of other highly protein-bound drugs.

Other analgesics including cyclooxygenase-2 selective inhibitor: Avoid concomitant use of two or more NSAIDs (including aspirin) as this may increase the risk of adverse effects (see section 4.4)

Anti-hypertensives: Reduced anti-hypertensive effect

Diuretics: Reduced diuretic effect. Diuretics can increase the risk of nephrotoxicity of NSAIDs.

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

Lithium: Decreased elimination of lithium

Methotrexate: Decreased elimination of methotrexate

Ciclosporin: Increased risk of nephrotoxicity

Anti-coagulants: 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)

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 a evidence of an increased risk of haemarthroses and haemtoma in HIV (+) haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.

Bilirubin tests can give a false positive result due to the presence of phenolic metabolites of Lodine in the urine.

Mifepristone: NSAIDs should not be used for 8-12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone.

Corticosteroids: increased risk of gastrointestinal ulceration or bleeding (see section 4.4)

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

Fertility:
The use of Lodine may impair female fertility and is not recommended in woman attempting to conceive. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of Lodine should be considered.

Pregnancy:
Drugs which inhibit prostaglandin biosynthesis may cause dystocia and delayed parturition as evidenced by studies in pregnant animals.
Congenital abnormalities have been reported in association with NSAID administration in man; however, these are low in frequency and do not appear to follow any discernible pattern. In view of the known effects of NSAIDs on the foetal

cardiovascular system, some inhibitors of prostaglandin biosynthesis have been shown to interfere with the risk of closure of the ductus arteriosus, use in the last trimester of pregnancy is contraindicated. 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).
From the 20th week of pregnancy onward, etodolac 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, etodolac should not be given unless clearly necessary. If etodolac 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 etodolac for several days from gestational week 20 onward. Etodolac 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 (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, etodolac is contraindicated during the third trimester of pregnancy (see section 4.3).

Lactation:
In limited studies so far available, NSAIDs can appear in breast milk in very low concentrations. NSAIDs should, if possible, be avoided when breastfeeding.

4.7 Effects on ability to drive and use machines

Lodine can cause dizziness, drowsiness, fatigue or abnormal vision. Patients need to be aware of how they react to this medicine before driving or operating machines.

4.8 Undesirable effects

Oedema, hypertension and cardiac failure, have been reported in association with NSAID treatment. Clinical trial and epidemiological data suggest that use of some NSAIDs (particularly at high doses and in long term treatment) may be associated with an increased

risk of arterial thrombotic events (for example myocardial infarction or stroke) (see section 4.4).

Gastrointestinal: Reported side effects include nausea, epigastric pain, diarrhoea, indigestion, heartburn, flatulence, abdominal pain, constipation, vomiting, ulcerative stomatitis, dyspepsia, haematemesis, melaena, rectal bleeding, exacerbation of colitis, vasculitis, headaches, dizziness, abnormal vision, pyrexia, drowsiness, tinnitus, rash, pruritus, fatigue, depression, insomnia, confusion, paraesthesia, tremor, weakness/malaise, dyspnoea**,** palpitations, bilirubinuria, hepatic function abnormalities and jaundice, urinary frequency, dysuria, angioedema, anaphylactoid reaction, photosensitivity, urticaria and Stevens-Johnson syndrome and Crohn's disease (See section 4.4) have been reported following administration. Less frequently, gastritis has been observed. Pancreatitis has been reported very rarely.

Hypersensitivity: Hypersensitivity reactions have been reported following treatment with NSAIDs. These may consists of (a) non-specific allergic reactions and anaphylaxis (b) respiratory tract reactivity comprising asthma, aggravated asthma, bronchospasm or dyspnoea, or (c) assorted skin disorders, including rashes of various types, pruritus, urticaria, purpura, angioedema and more rarely exfoliative and bullous dermatoses (including epidermal necrolysis and erythema multiforme).

Cardiovascular and cerebrovascular:
Oedema, hypertension and cardiac failure have been reported in association with NSAID treatment

Clinical trial and epidemiological data suggest that use of some NSAIDs (particularly at high doses and in long term treatment) may be associated with an increased risk of arterial thrombotic events (for example myocardial infarction or stroke) (see section 4.4).

Renal: Nephrotoxicity in various forms, including interstitial nephritis, nephrotic syndrome and renal failure.

Hepatic: abnormal liver function, hepatitis and jaundice

Neurological and special senses: Visual disturbances, optic neuritis, headaches, paraethesia, reports of aseptic meningitis (especially in patients with existing auto-immune disorders, such as systemic lupus erythematous, mixed connective tissue disease), with symptoms such as stiff neck, headache, nausea, vomiting, fever or disorientation (See section 4.4), depression, confusion, hallucinations, tinnitus, vertigo, dizziness, malaise, fatigue and drowsiness.

Haematological: Thrombocytopenia, neutropenia, agranulocytosis, aplastic anaemia and haemolytic anaemia.

Dermatological: Bullous reactions including Stevens Johnson Syndrome and Toxic Epidermal Necrolysis (very rare). Photosensitivity.

Skin and subcutaneous tissue disorders: Acute generalised exanthematous pustulosis (AGEP) (frequency not known). Fixed drug eruption (FDE) (frequency not known).

Immune system disorder: Anaphylactic reaction (frequency not known).

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

4.9 Overdose

(a) Symptoms
Symptoms include headache, nausea, vomiting, epigastric pain, gastrointaestinal bleeding, rarely diarrhoea, disorientation, excitation, coma, drowsiness, dizziness, tinnitus, fainting, occasionally convulsions. In cases of significant poisoning acute renal failure and liver damage are possible.

(b) Therapeutic measure
Patients should be treated symptomatically as required.
Within one hour of ingestion of a potentially toxic amount, activated charcoal should be considered. Alternatively, in adults, gastric lavage should be considered within one hour of indigestion of a potentially life-threatening overdose.
Good urine output should be ensured.
Renal and liver function should be closely monitored.
Patients should be observed for at least four hours after ingestion of potentially toxic amounts.
Frequent or prolonged convulsions should be treated with intravenous diazepam.
Other measures may be indicated by the patient's clinical condition.

The standard practices of gastric lavage, activated charcoal administration and general supportive therapy should be undertaken.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Inhibition of prostaglandin synthesis and COX-2 selectivity: All non-steroidal anti-inflammatory drugs (NSAIDs) have been shown to inhibit the formation of prostaglandins. It is this action which is responsible both for their therapeutic effects and some of their side-effects. The inhibition of prostaglandin synthesis observed with etodolac differs from that of other NSAIDs. In an animal model at an established anti-inflammatory dose, cytoprotective PGE concentration in the gastric mucosa have been shown to be reduced to a lesser degree and for a shorter period than other NSAIDs. This finding is consistent with subsequent *in-vitro* studies which have found etodolac to be selective for induced cyclo-oxygenase 2 (COX-2, associated with inflammation) over COX-1 (cytoprotective).

Furthermore, studies in human cell models have confirmed that etodolac is selective for the inhibition of COX-2.

The clinical benefit of preferential COX-2 inhibition over COX-1 has yet to be proven.

Anti-inflammatory effects: Experiments have shown etodolac to have marked anti-inflammatory activity, being more potent than several clinically established NSAIDs.

5.2 Pharmacokinetic properties

In man, etodolac is well absorbed following oral administration.

Etodolac is highly bound to serum proteins.

The elimination half-life averages seven hours in man. The primary route of excretion is in the urine, mostly in the form of metabolites.

In subjects receiving daily doses of Lodine SR 400mg or 600mg to steady state levels over a three day period, the peak plasma concentrations were 7.5µg/ml at 7.9 hours and 11.9µg/ml at 7.8 hours.

5.3 Preclinical safety data

Nothing of note to the prescriber.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydroxypropyl Methylcellulose
Dibasic Sodium Phosphate
Ethylcellulose
Lactose
Magnesium Stearate
Hydroxypropyl Cellulose
Macrogol 400
Macrogol 6000
Colourings - Titanium Dioxide (E171), Iron Oxide (E172)

6.2 Incompatibilities

None.

6.3 Shelf life

Lodine SR Tablets may be stored for up to 3 years.

6.4 Special precautions for storage

Store at room temperature, below 25^{o}C.

6.5 Nature and contents of container

Vinyl Aclar or PVdC/PVC/Aluminium foil blister packs of 2, 28 or 30 tablets.
HDPE bottle with child resistant closures of 28 or 30 tablets.
Polypropylene securitainers with polyethylene caps of 28 or 30 tablets.

6.6 Special precautions for disposal

None.

7. MARKETING AUTHORISATION HOLDER

Almirall, S.A.
Ronda General Mitre 151
08022 Barcelona
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8 MARKETING AUTHORISATION NUMBER(S)

PL 16973/0021

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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