IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0312/019/001
Case No: 2073612

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Transferred from PA0936/040/005.

Rosemont Pharmaceuticals

Rosemont House, **Yorkdale Industrial Park**, **Braithwaite Street**, **Leeds LS11 9XE**, **England**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Salazopyrin 250mg/5ml Oral Suspension

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **30/10/2009**.

Signed on behalf of the Irish Medicines Board this

_____

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Salazopyrin 250mg/5ml Oral Suspension.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Salazopyrin Oral Suspension contains 250mg Sulfasalazine in each 5ml.

Excipients:
Each 5 ml dose contains 1.55mg of sodium
Each 5 ml dose contains 6.10mg of ethanol
Each 5 ml dose contains 1.650g of sucrose

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral Suspension.
An orange-yellow coloured suspension with an orange/lemon flavour.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

a) Induction and maintenance of remission of ulcerative colitis; treatment of active Crohn's Disease.

b) Treatment of rheumatoid arthritis which has failed to respond to non-steroidal anti- inflammatory drugs (NSAIDs).

4.2 Posology and method of administration

Route of Administration
Take with food. Divide the dose through the day.
Oral.

Recommended Dosage
Ulcerative Colitis and Crohn's Disease:
Adults: Initial dosage is 1,000 to 2,000 mg four times daily for two to three weeks. As soon as remission has occurred the dose is reduced to 0.5 G three or four times daily. The interval between doses should not exceed eight hours.

Children: Initial dosage is 40 to 60 mg/kg b.w. daily.
Maintenance dosage is 20-30 mg/kg daily.

The oral and rectal routes can be used simultaneously in severe generalized ulcerative colitis of the rectum or rectosigmoid.

Rheumatoid Arthritis:
Adult Only: The usual initial dose is 0.5 G daily with weekly increments to a control level not exceeding 3 G daily.

4.3 Contraindications

Use in infants under the age of 2 years.

Use in patients where there is a known hypersensitivity to either sulfasalazine , its metabolites or any excipients as well as, sulfonamides and salicyaltes.

Use in patients with jaundice or porphyria.

4.4 Special warnings and precautions for use

Complete blood counts (including differential white cell, red cell and platelet cells), liver function tests and assessment of renal function (including urinalysis) should be performed in all patients initially and at least monthly for the first three months of treatment. Thereafter, monitoring should be performed as clinically indicated. The patient should also be counseled to report immediately with any sore throat, fever, malaise, pallor, purpura, jaundice or unexpected non-specific illness during sulfasalazine treatment as it may indicate myelosuppression, haemolysis or hepatoxicity. Treatment should be stopped immediately while awaiting the results of blood tests.

Sulfasalazine should not be given to patients with impaired hepatic or renal function or with blood dyscrasias, unless the potential benefit outweighs the risk.

Sulfasalazine should be given with caution to patients with severe allergy or bronchial asthma.

Use in children with systemic onset juvenile rheumatoid arthritis may result in a serum sickness-like reaction; therefore, sulfasalazine is not recommended in these patients.

Oral sulfasalazine inhibits the absorption and metabolism of folic acid and may cause folic acid deficiency (**see Section 4.6, Pregnancy and lactation**), potentially resulting in serious blood disorders (e.g., macrocytosis and pancytopenia). This can be normalized by the administration of folic acid or folinic acid (leucovorin).

Since sulfasalazine may cause haemolytic anaemia, it should be used with caution in patients with G-6-PD deficiency.

Because sulfasalazine causes crystalluria and kidney stone formation, adequate fluid intake should be ensured during administration.

Oligospermia and infertility may occur in men treated with sulfasalazine. Discontinuation of the drug appears to reverse these effects within 2 to 3 months.

Certain types of extended wear soft contact lenses may be permanently stained during therapy.

Salazopyrin Suspension contains Sucrose 1.65g/ 5ml. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Reduced absorption of digoxin, resulting in non-therapeutic serum levels, has been reported when used concomitantly with oral sulfasalazine.

Use of sulfonamides with folic-acid antagonists or hypoglycaemics may increase the effects of these agents

Due to inhibition of thiopurine methyltransferase (TPMT) by sulfasalazine, bone marrow suppression and leukopenia have been reported with thiopurine 6-mercaptopurine or its prodrug, azathioprine and oral sulfasalazine were used concomitantly.

Coadministration of oral sulfasalazine and methotrexate to rheumatoid arthritis patients did not alter the pharmacokinetic disposition of the drugs. However, an increased incidence of gastrointestinal adverse events,

especially nausea, was reported.

4.6 Pregnancy and lactation

Pregnancy

Reproduction studies in rats and rabbits have revealed no evidence of harm to the fetus. Published data regarding use of sulfasalazine in pregnant women have revealed no evidence of teratogenic hazards. If sulfasalazine is used during pregnancy, the possibility of fetal harm appears remote. Oral sulfasalazine inhibits the absorption and metabolism of folic acid and may cause folic acid deficiency. Because the possibility of harm cannot be completely ruled out, sulfasalazine should be used during pregnancy only if clearly needed.

Lactation

Sulfasalazine and sulfapyridine are found in low levels in breast milk. Caution should be used, particularly if breastfeeding premature infants or those deficient in G-6-PD

4.7 Effects on ability to drive and use machines

The effect of sulfasalazine on the ability to drive and use machinery has not been systematically evaluated.

4.8 Undesirable effects

Overall, about 75% of ADRs occur within three months of treatment, and over 90% by six months. Some unwanted effects are dose-dependent and symptoms can often be alleviated by reduction of the dose.

General

Sulfasalazine is split by intestinal bacteria to sulphapyridine and 5-amino salicylate so ADRs to either sulphonamide or salicylate are possible. Patients with slow acetylator status are more likely to experience ADRs related to sulphapyridine. The most commonly encountered ADRs are nausea, headache, loss of appetite and raised temperature.

Specific

The adverse reactions observed during clinical studies conducted with Sulfasalazine have been provided in a single list below by class and frequency (very common (≥ 1/10); common (≥1/100 to< 1/10); uncommon (≥ 1/1000 to < 1/100). Where an adverse reaction was seen at different frequencies in clinical studies, it was assigned to the highest frequency reported.

Additional reactions reported from post-marketing experience are included as frequency Not known (cannot be estimated from the available data) in the list below.

Body System	**Adverse drug reactions**
Infections and infestations	
Not known	Aseptic meningitis, parotitis, pseudomembranous colitis
Blood and Lymphatic System Disorders	
Common	Leukopenia
Uncommon	Thrombocytopenia*
Not known	Agranulocytosis, aplastic anemia, haemolytic anemia, Heinz body anaemia, hypoprothrombinaemia, lymphadenopathy, macrocytosis, megaloblastic anemia, methaemoglobinaemina, neutropenia, pancytopenia The risk of sulfasalazine-associated blood disorders is

	substantially higher in patients treated for rheumatoid arthritis than it is in patients treated for inflammatory bowel disease.
Immune System Disorders:	
Not known	Anaphylaxis, polyarteritis nodosa, serum sickness
Metabolism and Nutrition Disorders:	
Not known	Loss of appetite
Psychiatric Disorders:	
Uncommon	Depression
Not known	Hallucinations, insomnia
Nervous System Disorders:	
Common	Dizziness, headache, taste disorders
Not known	Ataxia, convulsions, encephalopathy, peripheral neuropathy, smell disorders
Ear and Labyrinth Disorders:	
Common	Tinnitus
Not known	Vertigo
Eye Disorders:	
Not known	Conjuctivial and scleral infection
Cardiac Disorders:	
Not known	Allergic myocarditis, cyanosis, pericarditis
Vascular Disorders:	
Not known	Vasculitis
Congenital, familial and Genetic Disorders:	
Not known	Acute attack may be precipitated in patients with prophyria**
Respiratory, Thoracic and Mediastinal Disorders:	
Common	Cough
Uncommon	Dyspnoea
Not known	Fibrosing alveolitis, eosinophilic infiltration, interstitial lung disease
Gastrointestinal Disorders:	
Very Common	Gastric distress, nausea
Uncommon	Abdominal pain, diarrhoea, vomiting
Not known	Aggravation of ulcerative colitis, pancreatitis, stomatitis
Hepato-biliary Disorders:	
Not known	Hepatic failure, fulminant hepatitis, hepatitis*
Skin and Subcutaneous Tissue Disorders:	
Common	Pruritus
Uncommon	Alopecia, urticaria
Not known	Epidermal necrolysis (Lyell's syndrome), Stevens-Johnson syndrome, drug rash with eosinophilia and systemic symptoms (DRESS), toxic pustuloderma, erythema, exanthema,

	exfoliative dermatitis, periorbital oedema, lichen planus, photosensitivity
Musculoskeletal and Connective Tissue Disorders:	
Common	Arthralgia
Not known	Systemic lupus erythematosus, Sjögren's syndrome
Renal and Urinary Disorders:	
Common	Proteinuria
Not known	Crystalluria*, haematuria, Nephrotic syndrome, interstitial nephritis
Reproductive System and Breast Disorders:	
Not known	Reversible oligospermia*
General Disorders and Administration Site Conditions:	
Common	Fever
Uncommon	Facial oedema
Not known	Drug fever, yellow discoloration of skin and body fluids, generalised skin eruptions
Investigations:	
Uncommon	Elevation of liver enzymes
Not known	Induction of autoantibodies

* See Section 4.4 for further information
** See section 4.3 for further information

4.9 Overdose

The most common symptoms of overdose, similar to other sulfonamides, are nausea and vomiting . Patients with impaired renal function are at increased risk of serious toxicity. Treatment is symptomatic and should be supportive, including alkalinisation of urine. Patients should be observed for development of methemoglobinemia or sulfahemoglobinemia. If these occur treat appropriately.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Sulfasalazine is split bacterially in the colon into sulfapyridine and mesalazine and all three compounds have pharmacological effects, principally immunomodulatory, antibacterial, alteration of the arachidonic acid cascade and the activity of certain enzymes.

5.2 Pharmacokinetic properties

Around 90% of a sulfasalazine (SASP) dose reaches the colon where bacteria split the drug into sulfapyridine (SP) and mesalazine (Me). Most SP is absorbed, hydroxylated or glucuronidated and a mix of unchanged and metabolised SP appears in the urine. Some Me is taken up and acetylated in the colon wall, such that renal excretion is mainly AC-Me. SASP is excreted unchanged in the bile and urine.

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Xanthan gum (E415)
Sodium benzoate (E211)
Polysorbate 80
Orange/lemon flavour (PFC 8432)
- Contains Sucrose
Ethanol
Sodium Chloride

Avicel RC591 (microcrystalline cellulose (E460) and carmellose sodium (E466))
Hydrochloric Acid (for pH adjustment)
Sodium Hydroxide (for pH adjustment)
Sucrose
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

30 months.

6.4 Special precautions for storage

Do not store above 25°C. The bottle should be protected from light.

6.5 Nature and contents of container

Natural HDPE bottle containing 500ml of suspension sealed with a Polypropylene child resistant squeeze lock cap.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Shake well before use.
Any unused product should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Rosemont Pharmaceuticals Limited
Rosemont House
Yorkdale Industrial Park
Braithwaite Street
Leeds
LS11 9XE
UK

8 MARKETING AUTHORISATION NUMBER

PA 312/19/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 13 July 1998

Date of last renewal: 13 July 2008

10 DATE OF REVISION OF THE TEXT

October 2009