PROFESSIONAL INFORMATION

SCHEDULING STATUS

S2

1 NAME OF THE MEDICINE

ECOTRIN 81 mg enteric coated tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains aspirin (acetylsalicylic acid) 81 mg.

Sugar free.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Enteric coated tablet.

Convex, round, orange, coated tablet with a black curved “Ecotrin low” monogram on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

To reduce the risk of myocardial infarction in patients with unstable angina or in patients who have had a previous myocardial infarction. To reduce the risk of recurrent transient ischaemic attacks or stroke in men who have had transient ischaemia of the brain due to fibrin platelet emboli. To reduce the risk of graft occlusion following aorta coronary by-pass surgery.

4.2 Posology and method of administration

Posology

Adults: One to three tablets as directed by your doctor to be taken every day, preferably at the same time each day.

Warning: The optimal dose for inhibition of platelet aggregation in humans is not known. Do not use this medicine for indications related to the inhibition of platelet aggregation unless directed by a doctor.

Method of administration

For oral use.

4.3 Contraindications

- Hypersensitivity to aspirin, salicylic acid compounds or prostaglandin synthetase inhibitors (e.g. certain asthma patients who may suffer an attack or faint), or to any of the excipients (see section 6.1).
- Active, or history of recurrent peptic ulcer and/or gastric/intestinal haemorrhage, or other kinds of bleeding such as cerebrovascular haemorrhages.
- Should not be administered to patients with haemorrhagic diathesis; coagulation disorders such as haemophilia and thrombocytopenia.
- Severe hepatic impairment.
- Severe renal impairment.
- Gout.
- Severe cardiac insufficiency.
- Methotrexate used at doses >15mg/week (see section 4.5).
- Aspirin should not be taken during the first and third trimesters of pregnancy and during lactation.
- Aspirin should be discontinued one week before scheduled surgical procedures.
- In the event of overdosage and notwithstanding the fact that the person may be asymptomatic, the nearest doctor, hospital, or Poison Control Centre must be contacted immediately.
- Do not exceed the recommended daily dose.

4.4 Special warnings and precautions for use

If symptoms persist consult your doctor. Do not use continuously for more than 10 days without consulting your doctor.

Aspirin has been implicated in Reye's syndrome, a rare but serious illness in children and teenagers with chickenpox and influenza. A doctor should be consulted before aspirin is used in such patients.

There is an increased risk of haemorrhage and prolongation of bleeding time particularly during or after surgery (even in cases of minor procedures, e.g. tooth extraction). Use with caution before surgery, including tooth extraction. Temporary discontinuation of treatment may be necessary.

ECOTRIN 81 mg is not recommended during menorrhagia where it may increase menstrual bleeding.

ECOTRIN 81 mg is to be used with caution in cases of uncontrolled hypertension and when patients have a past history of gastric or duodenal ulcer or haemorrhagic episodes or are undergoing therapy with anticoagulants.

Patients should report any unusual bleeding symptoms to their medical practitioner. If gastrointestinal bleeding or ulceration occurs the treatment should be withdrawn.

Acetylsalicylic acid should be used with caution in patients with moderately impaired renal or hepatic function (contraindicated if severe), or in patients who are dehydrated since the use of NSAIDs may result in deterioration of renal function. Liver function tests should be performed regularly in patients presenting slight or moderate hepatic insufficiency.

Acetylsalicylic acid may promote bronchospasm and asthma attacks or other hypersensitivity reactions. Risk factors are existing asthma, hay fever, nasal polyps or chronic respiratory diseases. The same applies for patients who also show allergic reaction to other substances (e.g. with skin reactions, itching or urticaria).

Serious skin reactions, including Steven-Johnsons syndrome, have less frequently been reported in association with the use of acetylsalicylic acid (see section 4.8). ECOTRIN 81 mg should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Elderly patients are particularly susceptible to the adverse effects of NSAIDs, including acetylsalicylic acid especially gastrointestinal bleeding and perforation which may be fatal. Where prolonged therapy is required, patients should be reviewed regularly.

Concomitant treatment with ECOTRIN 81 mg and other medicines that alter haemostasis (i.e. anticoagulants such as warfarin, thrombolytic and antiplatelet medicines, anti-inflammatory medicines and selective serotonin reuptake inhibitors) is not recommended, unless strictly indicated, because they may enhance the risk of haemorrhage (see section 4.5). If the combination cannot be avoided, close observation for signs of bleeding is recommended.

Caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration, such as oral corticosteroids, selective serotonin-reuptake inhibitors and deferasirox (see section 4.5).

Acetylsalicylic acid should be avoided in early and late pregnancy and generally during breast feeding (see sections 4.3 and 4.6).

Acetylsalicylic acid in low doses reduces uric acid excretion. Due to this fact, patients who tend to have reduced uric acid excretion may experience gout attacks (see section 4.5).

The risk of hypoglycaemic effect with sulfonylureas and insulins may be potentiated with ECOTRIN 81 mg taken at over dosage (see section 4.5).

Aspirin should be used with caution in patients with glucose-6-phosphate dehydrogenase deficiency.

Drug Reaction with Eosinophillia and Systemic Symptoms (DRESS) has been reported in patients taking NSAIDs such as ECOTRIN 81 mg. Some of these

events have been fatal or life-threatening. DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling. Other clinical manifestations may include hepatitis, nephritis, haematological abnormalities, myocarditis, or myositis. Sometimes symptoms of DRESS may resemble an acute viral infection. Eosinophillia is often present. Because this disorder is variable in its presentation, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, discontinue ECOTRIN 81 mg and evaluate the patient immediately.

4.5 Interaction with other medicines and other forms of interaction

Contraindicated combinations

Methotrexate (used at doses >15 mg/week)

The combined medicines, methotrexate and acetylsalicylic acid, enhance haematological toxicity of methotrexate due to the decreased renal clearance of methotrexate by acetylsalicylic acid. Therefore, the concomitant use of methotrexate (at doses >15 mg/week) with ECOTRIN 81 mg is contraindicated (see section 4.3).

Not recommended combinations

Uricosuric medicines, e.g. probenecid, sulfinpyrazone

Salicylates reverse the effect of probenecid and sulfinpyrazone. The combination should be avoided.

Combinations requiring precautions for use or to be taken into account

Anticoagulants and thrombolytics e.g. coumarin, heparin, warfarin, alteplase

Increased risk of bleeding due to inhibited thrombocyte function, injury of the duodenal mucosa and displacement of oral anticoagulants from their plasma protein binding sites. The bleeding time should be monitored (see section 4.4). Particularly, treatment with acetylsalicylic acid should not be initiated within the first 24 hours after treatment with alteplase in acute stroke patients. Concomitant use is therefore not recommended.

Anti-platelet medicines (e.g. clopidogrel, ticlopidine, cilostazol and dipyridamole) and selective serotonin reuptake inhibitors (SSRIs; such as sertraline or paroxetine)

Increased risk of gastrointestinal bleeding (see section 4.4).

Antidiabetics, e.g. sulfonylureas and insulin

Salicylics may increase the hypoglycaemic effect of antidiabetics. Thus, some downward readjustment of the dosage of the antidiabetic may be appropriate if large doses of salicylates are used. Increased blood glucose controls are recommended.

Digoxin and lithium

Acetylsalicylic acid impairs the renal excretion of digoxin and lithium, resulting in increased plasma concentrations. Monitoring of plasma concentrations of digoxin and lithium is recommended when initiating and terminating treatment with acetylsalicylic acid. Dose adjustment may be necessary.

Diuretics and antihypertensives

NSAIDs may decrease the antihypertensive effects of diuretics and other antihypertensive medicines. Blood pressure should be well monitored. [(2)]

Concomitant administration with ACE-inhibitors, angiotensin II receptor antagonists and calcium channel blocker increases the risk of acute renal insufficiency in combination with high-dose ASA.

Diuretics: Risk of acute renal failure due to the decreased glomerual filtration via decreased renal prostaglandin synthesis. Hydrating the patient and monitoring renal function at the start of the treatment is recommended. In case of association with verapamil the bleeding time should be monitored.

Carbonic anhydrase inhibitors (acetazolamide)

May result in severe acidosis and increased central nervous system toxicity.

Systemic corticosteroids

The risk of gastrointestinal ulceration and bleeding may be increased when acetylsalicylic acid and corticosteroids are co-administered (see section 4.4).

Methotrexate (used at doses <15 mg/week)

The combined medicines, methotrexate and acetylsalicylic acid, may increase haematological toxicity of methotrexate due to decreased renal clearance of methotrexate by acetylsalicylic acid. Weekly blood count checks should be done during the first weeks of the combination. Enhanced monitoring should take place in the presence of even mildly impaired renal function, as well, as in elderly.

Other NSAIDs

Increased risk of ulcerations and gastrointestinal bleeding due to synergistic effects.

Ibuprofen

Experimental data suggest that ibuprofen may inhibit the effect of low dose acetylsalicylic acid on platelet aggregation when they are dosed concomitantly. However, the limitations of these data and the uncertainties regarding extrapolation of *ex vivo* data to the clinical situation imply that no firm conclusions can be made for regular ibuprofen use, and no clinically relevant effect is considered to be likely for occasional ibuprofen use (see section 5.1).

Metamizole

Metamizole may reduce the effect of acetylsalicylic acid on platelet aggregation, when taken concomitantly. Therefore, this combination should be used with caution in patients taking low dose aspirin for cardio protection.

Ciclosporin, tacrolimus

Concomitant use of NSAIDs and ciclosporin or tacrolimus may increase the nephrotoxic effect of ciclosporin and tacrolimus. The renal function should be monitored in case of concomitant use of these medicines and acetylsalicylic acid.

Antacids

The excretion of acetylsalicylic acid is increased by alkaline urine, which can occur with some antacids.

Valproate

Acetylsalicylic acid has been reported to decrease the binding of valproate to serum albumin, thereby increasing its free plasma concentrations at steady state.

Phenytoin

Salicylate diminishes the binding of phenytoin to plasma albumin. This may lead to decreased total phenytoin levels in plasma, but increased free phenytoin fraction. The unbound concentration, and thereby the therapeutic effect, does not appear to be significantly altered.

Alcohol

Concomitant administration of alcohol and acetylsalicylic acid increases the risk of gastrointestinal bleeding.

4.6 Fertility, pregnancy and lactation

Pregnancy

ECOTRIN 81 mg is contraindicated in the first and third trimester of pregnancy (see section 4.3).

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

- cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension);
- renal dysfunction, which may progress to renal failure with oligo- hydroamniosis;

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.

Breastfeeding

Low quantities of salicylates and of their metabolites are excreted into the breast milk. Since adverse effects for the infant have not been reported up to now, short-term use of the recommended dose does not require suspending lactation. In

cases of long-term use and/or administration of higher doses, breastfeeding should be discontinued.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed with ECOTRIN 81 mg. Based on the pharmacodynamic properties and the side effects of acetylsalicylic acid, no influence on the reactivity and the ability to drive or use machines is expected.

4.8 Undesirable effects

a. Summary of the safety profile

The most common adverse affects occurring with therapeutic doses of aspirin are gastrointestinal disturbances such as dyspepsia, nausea, vomiting, diarrhoea.

b. Tabulated summary of adverse reactions

Side effects are grouped on the basis of System Organ Class. Within each system organ class the frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000) and not known (cannot be estimated from the available data).

MedDRA system organ class	**Frequency**	**Adverse reactions**
Blood and lymphatic system disorders	Common	Increased bleeding tendencies.
	Rare	Thrombocytopenia, granulocytosis, aplastic anaemia.
	Not known	Cases of bleeding with prolonged bleeding time such as epistaxis, gingival bleeding. Symptoms may

MedDRA system organ class	**Frequency**	**Adverse reactions**
		persist for a period of 4–8 days after acetylsalicylic acid discontinuation. As a result there may be an increased risk of bleeding during surgical procedures. Existing (haematemesis, melaena) or occult gastrointestinal bleeding, which may lead to iron deficiency anaemia (more common at higher doses).
Immune system disorders	Rare	Hypersensitivity reactions, angio-oedema, allergic oedema, anaphylactic reactions including shock.
Metabolism and nutrition disorders	Not known	Hyperuricemia, hypoglycaemia.
Nervous system disorders	Rare	Intracranial haemorrhage.
	Not known	Headache, vertigo.
Ear and labyrinth disorders	Not known	Reduced hearing ability; tinnitus.
Vascular disorders	Rare	Haemorrhagic vasculitis.
Respiratory, thoracic and mediastinal disorders	Uncommon	Rhinitis, dyspnoea.
	Rare	Bronchospasm, asthma attacks.
Gastrointestinal disorders	Common	Dyspepsia, nausea, vomiting, diarrhoea.
	Rare	Severe gastrointestinal haemorrhage.
	Not known	Gastric or duodenal ulcers and

MedDRA system organ class	**Frequency**	**Adverse reactions**
		perforation.
Hepato-biliary disorders	Rare	Reye's syndrome.
	Not known	Hepatic insufficiency, hepatic enzyme increased.
Skin and subcutaneous tissue disorders	Uncommon	Urticaria.
	Rare	Steven-Johnsons syndrome, Lyell's syndrome, purpura, erythema nodosum, erythema multiforme.
	Not known	Drug Reaction with Eosinophillia and Systemic Symptoms (DRESS) (see section 4.4)
Renal and urinary disorders	Not known	Impaired renal function, salt and water retention.
Reproductive system and breast disorders	Rare	Menorrhagia.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Form**", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Mild chronic salicylate intoxication usually occurs only after repeated administration of large doses. Symptoms include dizziness, tinnitus, deafness, sweating, nausea, headache, vomiting and mental confusion.

Symptoms of more acute or severe intoxication following overdosage include hyperventilation, fever, restlessness, ketosis, respiratory alkalosis and metabolic acidosis.

Depression of the central nervous system may lead to coma; cardiovascular collapse or respiratory failure.

In children drowsiness and metabolic acidosis commonly occur, hypoglycaemia may be severe.

In cases of overdosage consult a doctor immediately.

Gastric lavage, fluid and electrolyte management is the mainstay of treatment with the immediate aim being correction of acidosis, hyperpyrexia, hypokalaemia and dehydration.

Salicylate remaining in the stomach may be adsorbed by activated charcoal. Alkaline diuresis, haemodialysis or haemoperfusion are effective methods of removing salicylate from the plasma.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 8 Medicines acting on the blood and haemopoietic system.

Pharmacotherapeutic group: Antithrombotic agents: platelet aggregation inhibitors excl. heparin, ATC code: B01AC06.

Ecotrin inhibits platelet aggregation by inactivation of platelet cyclo-oxygenase, the enzyme that produces the cyclic endoperoxide precursor of thromboxane A2.

5.2 Pharmacokinetic properties

Absorption

After oral administration, acetylsalicylic acid is rapidly and completely absorbed from the gastrointestinal tract. The principal site of absorption is the proximal small intestine. However, a significant portion of the dosage is already hydrolysed to salicylic acid in the intestinal wall during the absorption process. The degree of hydrolysis is dependent on the rate of absorption. After intake of aspirin tablets the maximum plasma levels of acetylsalicylic acid and salicylic acid are reached after about 20 minutes and 1 hour, respectively, following administration in the fasted state.

Distribution

Acetylsalicylic acid as well as the main metabolite salicylic acid, are extensively bound to plasma proteins, primarily albumin, and distributed rapidly into all parts of the body. Maximum plasma concentration is reached after 0,3 – 2 hours (total salicylate). The degree of protein binding of salicylic acid is strongly dependant of both the salicylic acid and albumin concentration. The volume of distribution of acetylsalicylic acid is ca. 0,16 l/kg of body weight. Salicylic acid slowly diffuses into the synovial fluid, crosses the placental barrier and passes into breast milk.

Biotransformation

Acetylsalicylic acid is rapidly metabolised to salicylic acid, with a half-life of 15-30 minutes. Salicylic acid is subsequently predominantly converted into glycine and glucuronic acid conjugates.

Elimination kinetics of salicylic acid is dose-dependent, because the metabolism is limited by liver enzyme capacity. Thus, elimination half-time varies and is 2-3 hours after low doses, 12 hours after usual analgesic doses and 15-30 hours after high therapeutic doses or intoxication.

Elimination

Salicylic acid and its metabolites are predominantly excreted via the kidneys.

5.3 Preclinical safety data

The nonclinical safety profile of acetylsalicylic acid is well documented.

In experimental animal studies, salicylates have shown no other organ injury than renal damage. In rat studies, fetotoxicity and teratogenic effects were observed with acetylsalicylic acid at maternotoxic doses. Clinical relevance is unknown as the doses used in non-clinical studies are much higher (7 times at least) than the maximal recommended doses in targeted cardiovascular indications. Acetylsalicylic acid was extensively investigated with regard to mutagenic and carcinogenic effects. The results as a whole show no relevant signs for any mutagenic or carcinogenic effects in mice and rat studies.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Carnauba wax

Corn starch

Colloidal silicon dioxide

Methacrylic copolymer

Microcrystalline cellulose

Opacode monogramming ink black

Opadry clear

Opadry YS-1-6223, orange

Propylene glycol

Stearic acid

Simethicone

Triethyl citrate

Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 25 ºC in a dry place.

6.5 Nature and contents of container

- 30 ml or 50 ml white HDPE bottles fitted with a white polypropylene screw on cap. A desiccant and foam plug is included in each pack.
- Aluminium/Aluminium blister strips of 10 tablets per strip with 3 blister strips packed in an outer unit cartons.

Pack sizes of 30; 50 and 100 tablets.

6.6 Special precautions for disposal and other handling

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

ACINO PHARMA (PTY) LTD.

106 16th Road

Midrand, 1686

Gauteng

South Africa

8 REGISTRATION NUMBER

29/2.7/0767

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21 June 1996

10 DATE OF REVISION OF THE TEXT

02 February 2023