Loprin®
(Aspirin)

Highnoon

COMPOSITION
Loprin 75mg Tablet:
Each enteric-coated tablet contains Aspirin 75mg
Loprin 150mg Tablet:
Each enteric-coated tablet contains Aspirin 150mg

DESCRIPTION
Aspirin is a salicylate Non-steroidal anti-inflammatory drug (NSAID) and has many properties in common with non-aspirin NSAID. Aspirin and other salicylates have analgesic, anti-inflammatory and anti-pyretic properties. Aspirin also inhibits platelet aggression while non-acetylated salicylates do not.

MECHANISM OF ACTION
Aspirin (acetylsalicylic acid) is an inhibitor of both prostaglandin synthesis and platelet aggregation. Aspirin inhibits platelet aggregation by irreversible inhibition of platelet cyclooxygenase and thus inhibits the generation of thromboxane A2, a powerful inducer of platelet aggregation and vasoconstriction. The differences in activity between aspirin and salicylic acid are thought to be due to the acetyl group on the aspirin molecule. This acetyl group is responsible for the inactivation of cyclo-oxygenase via acetylation.

PHARMACOKINETICS
Aspirin and other salicylates are absorbed rapidly from the gastrointestinal tract when taken orally but absorption after rectal doses is less reliable. Aspirin and other salicylates can also be absorbed through the skin. After oral doses, absorption of non-ionised aspirin occurs in the stomach and intestine. Some aspirin is hydrolysed to salicylate in the gut wall. Once absorbed, aspirin is rapidly converted to salicylate, but during the first 20 minutes after an oral dose aspirin is the main form of the drug in the plasma. Aspirin is 80 to 90% bound to plasma proteins and is widely distributed; its volume of distribution is reported to be 170mL/kg in adults. As plasma-drug concentrations increase, the binding sites on the proteins become saturated and the volume of distribution increases. Both aspirin and salicylate have pharmacological activity although only aspirin has an anti-platelet effect. Salicylate is extensively bound to plasma proteins and is rapidly distributed to all body parts. Salicylates appears in the breast milk and crosses the placenta.

Salicylate is mainly eliminated by hepatic metabolism; the metabolites include salicyluric acid, salicyl phenolic glucuronide, salicylic acyl glucuronide, gentisic acid, and gentisuric acid. The formation of the major metabolites, salicyluric acid and salicyl phenolic glucuronide, is easily saturated and follows Michaelis-Menten kinetics; the other metabolic routes are first-order processes. As a result, steady-state plasma-salicylate concentrations increase disproportionately with dose. After a 325-mg aspirin dose elimination is a first-dose process and the plasma-salicylate half-life is about 2 to 3 hours; at high aspirin doses, the half-life increases to 15 to 30 hours. Salicylate is also excreted unchanged in the urine; the amount excreted by this route increases with increasing dose and also depends on urinary pH, about 30% of a dose being vexcreted in alkaline urine compared with 2% of a dose in excreted urine. Renal excretion involves glomerular filtration, active renal tubular secretion, and passive tubular reabsorption. Salicylate is removed by haemodialysis.

INDICATIONS
- Cardiovascular disease (secondary prevention)
- Management of Unstable angina and non-ST-segment elevation myocardial infarction (NSTEMI).
  Management of ST-segment elevation myocardial infarction (STEMI)
- Suspected transient ischaemic attack
- Transient ischaemic attack, Ischaemic stroke not associated with atrial fibrillation
- Acute ischaemic stroke
- Atrial fibrillation following a disabling ischaemic stroke (before being considered for anticoagulant treatment)
- Following disabling ischaemic stroke in patients receiving anticoagulation for a prosthetic heart valve and who are at significant risk of haemorrhagic transformation
- Following Coronary by-pass surgery

DOSAGE AND ADMINISTRATION
Loprin 75mg and Loprin 150mg are to be taken by mouth.
- Cardiovascular disease (secondary prevention)
  Adult: 75 mg daily
- Management of Unstable angina and non-ST-segment elevation myocardial infarction (NSTEMI). Management of ST-segment elevation myocardial infarction (STEMI)

  Adult: 300 mg, chewed or dispersed in water
- Suspected transient ischaemic attack

  Adult: 300 mg once daily until diagnosis established
- Transient ischaemic attack (long-term treatment in combination with dipyridamole Ischaemic stroke not associated with atrial fibrillation (in combination with dipyridamole if clopidogrel contra-indicated or not tolerated), Ischemic stroke not associated with atrial fibrillation (used alone if clopidogrel and dipyridamole contra-indicated or not tolerated)

  Adult: 75 mg once daily
- Acute ischaemic stroke

  Adult: 300mg once daily for 14 days, to be initiated 24 hours after thrombolysis or as soon as possible within 48 hours of symptom onset in patients not receiving thrombolysis
- Atrial fibrillation following a disabling ischaemic stroke (before being considered for anticoagulant treatment)

  Adult: 300 mg once daily for 14 days
- Following disabling ischaemic stroke in patients receiving anticoagulation for a prosthetic heart valve and who are at significant risk of haemorrhagic transformation

  Adult: 300mg once daily, anticoagulant treatment stopped for 7 days and to be substituted with aspirin.
- Following disabling ischaemic stroke in patients receiving anticoagulation for a prosthetic heart valve and who are at significant risk of haemorrhagic transformation
  Adult: 300 mg once daily, anticoagulant treatment stopped for 7 days and to be substituted with aspirin
- Following Coronary by-pass surgery
  Adult: 75-300 mg daily

CONTRAINDICATIONS
Contraindications of Aspirin are:
- Hypersensitivity to salicylic acid compounds or prostaglandin synthetase inhibitors (e.g. certain asthma patients who may suffer an attack or rhinitis and certain patients who may suffer from bronchospasm, rhinitis and urticaria) and to any of the excipients
- Peptic ulceration or history of peptic ulceration and/or gastric/intestinal haemorrhage, or other kinds of bleeding such as cerebrovascular haemorrhages
- Severe hepatic impairment
- Severe renal impairment
- Gout
- Children under 16 (except under medical supervision for use for example in juvenile rheumatoid arthritis)
- Doses >100 mg/day during the third trimester of pregnancy
- Breast feeding
- Haemorrhagic diathesis; coagulation disorders such as haemophilia and thrombocytopenia and where there is concurrent anti-coagulant therapy

ADVERSE EFFECTS
The reported adverse event are: gastrointestinal disturbances such as dyspepsia, nausea, vomiting. irritation of the gastric mucosa with erosion, ulceration, haematemesis, melaena, increase bleeding tendencies, bleeding time, decrease platelet adhesiveness, thrombocytopenia, granulocytosis, aplastic anaemia, intracranial haemorrhage , existing (haematemesis, melaena) or occult gastrointestinal bleeding, may lead to iron deficiency anaemia (more common at higher doses), Steven-Johnsons syndrome, Lyells syndrome, purpura, erythema nodosum, erythema multiforme, haemorrhagic vasculitis, menorrhagia, hepatotoxicity, dizziness, tinnitus, deafness, sweating, headache, confusion, symptoms of severe intoxication include hyperventilation, fever, restlessness, ketosis and respiratory alkalosis and metabolic acidosis. Cardiovascular collapse and respiratory failure may also occur. In children drowsiness and metabolic acidosis commonly occur, hypoglycemia may be severe. In asthma patient; chronic urticarial or chronic rhinitis, exhibit hypersensitivity to aspirin which may provoke reactions including urticaria and other skin eruptions, angioedema, rhinitis and severe, even fatal paroxysmal bronchospasm and dyspnoea. Hypersensitivity reactions, allergic oedema, anaphylactic reactions including shock have rarely occurred.

DRUG INTERACTION
Contraindicated Combinations
Methotrexate (used at doses >15 mg/week):
The combined drugs, 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 Aspirin 75 mg is contraindicated.
Not recommended combinations
Uricosuric agents, e.g, probenecid and sulfinpyrazone, Salicylates reverse the effect of probenecid. The combination should be avoided.
Combinations requiring precautions for use or to be taken into account
- Anticoagulants e.g. coumarin, heparin, warfarin 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.
- Antidiabetics, e.g. sulphonylureas
  - o Salicylics may increase the hypoglycaemic effect of sulphonylureas.
- Anti-platelet agents (e.g clopidogrel, ticlopidine and dipyridamole) and selective serotonin reuptake inhibitors (SSRIs; such as sertraline or paroxetine)
  - o Increased risk of gastrointestinal bleeding.
- Diuretics and antihypertensives
  - o NSAIDs may decrease the antihypertensive effects of diuretics and other antihypertensive agents. As for other NSAIDs concomitant administration with ACE-inhibitors increases the risk of acute renal insufficiency.
  - o 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.
  - o Aspirin antagonises the diuretic effect of spironolactone.
- Systemic corticosteroids
  - o The risk of gastrointestinal ulceration and bleeding may be increased when acetylsalicylic acid and corticosteroids are co-administered.
- Digoxin and lithium
  - o Acetylsalicylic acid impairs the renal excretion of digoxin and lithium, resulting in increased plasma concentrations. Monitoring plasma concentrations of digoxin and lithium is recommended when initiating and terminating treatment with acetylsalicylic acid. Dose adjustment may be necessary
- Carbonic anhydrase inhibitors (acetazolamide)
  - o May result in severe acidosis and increased central nervous system toxicity
- Methotrexate (used at doses <15 mg/week)
  - o The combined drugs, 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.
- Other NSAIDs
  - o Increased risk of ulcerations and gastrointestinal bleeding due to synergistic effects.
- Ibuprofen
  - o Experimental data suggest that ibuprofen may inhibit the effect of low dose aspirin 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.
- Ciclosporin, tacrolimus
  - o 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 agents and acetylsalicylic acid.
- Valproate
  - o Acetylsalicylic acid has been reported to decrease the binding of valproate to serum albumin, thereby increasing its free plasma concentrations at steady state.
- Phenytoin
  - o 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
  - o Concomitant administration of alcohol and acetylsalicylic acid increases the risk of gastrointestinal bleeding.
- Antacids will reduce the effect of aspirin. Principle incompatibilities are iron salts, carbonates and alkali hydroxides.
- Metoclopramide potentiates the effect of aspirin.

WARNINGS AND PRECAUTIONS
- Aspirin 75 mg is not suitable for use as an anti-inflammatory/analgesic/antipyretic
- Before commencing long-term aspirin therapy for the management of cardiovascular or cerebrovascular disease patients should consult their doctor who can advise on the relative benefits versus the risks for the individual patient.
- Administer with caution in the presence of allergic disease, renal or hepatic impairment and dehydration. Liver tests should be performed regularly in patients presenting slight or moderate hepatic insufficiency.
- There is a possible association between Aspirin and Reye's Syndrome when given to children. Reye's syndrome is a very rare disease, which affects the brain and liver, and can be fatal for this reason aspirin should not be given to children under 16 years unless specifically indicated (e.g. for Kawasaki's disease).
- There is an increased risk of haemorrhage particularly during or after operative procedures (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.
- Aspirin 75 mg is not recommended during menorrhagia where it may increase menstrual bleeding.
- Aspirin 75 mg is to be used with caution in cases of 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 physician. If gastrointestinal bleeding or ulceration occurs the treatment should be withdrawn.
- 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 rarely been reported in association with the use of acetylsalicylic acid. Aspirin 75 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 Aspirin 75 mg and other drugs that alter haemostasis (i.e. anticoagulants such as warfarin, thrombolytic and antiplatelet agents, anti-inflammatory drugs and selective serotonin reuptake inhibitors) is not recommended, unless strictly indicated, because they may enhance the risk of haemorrhage. 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.
- 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.
- The risk of hypoglycaemic effect with sulfonylureas and insulins may be potentiated with Aspirin 75 mg taken at over dosage.
- Aspirin 75 mg contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

USED IN SPECIAL POPULATION
Pregnancy
Low doses (up to 100 mg/day): Clinical studies indicate that doses up to 100 mg/day for restricted obstetrical use, which require specialised monitoring, appear safe.

Doses of 100 - 500 mg/day and above: There is insufficient clinical experience regarding the use of doses above 100 mg/day up to 500 mg/day. Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1%, up to approximately 1,5 %. The risk is believed to increase with dose and duration of therapy. In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-foetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period. During the first and second trimester of pregnancy, acetylsalicylic acid should not be given unless clearly necessary. If acetylsalicylic acid 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.

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.

Consequently, acetylsalicylic acid at doses of 100 mg/day and higher is contraindicated during the third trimester of pregnancy.

Lactation
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.

OVERDOSAGE
Salicylate poisoning is usually associated with plasma concentrations >350 mg/L (2.5 mmol/L). Most adult deaths occur in patients whose concentrations exceed 700 mg/L (5.1 mmol/L). Single doses less than 100 mg/kg are unlikely to cause serious poisoning.

Symptoms: Common features of salicylate poisoning include vomiting, dehydration, tinnitus, vertigo, deafness, sweating, warm extremities with bounding pulses, increased respiratory rate and hyperventilation. Some degree of acid-base disturbance is present in most cases.

A mixed respiratory alkalosis and metabolic acidosis with normal or high arterial pH (normal or reduced hydrogen ion concentration) is usual in adults and children over the age of 4 years. In children aged 4 years or less, a dominant metabolic acidosis with low arterial pH (raised hydrogen ion concentration) is common. Acidosis may increase salicylate transfer across the blood brain barrier.

Uncommon features of salicylate poisoning include haematemesis, hyperpyrexia, hypoglycaemia, hypokalaemia, thrombocytopaenia, increased INR/PTR, intravascular coagulation, renal failure and non-cardiac pulmonary oedema.
Central nervous system features including confusion, disorientation, coma and convulsions, are less common in adults than in children.

Management: Give activated charcoal if an adult presents within one hour of ingestion of more than 250 mg/kg. The plasma salicylate concentration should be measured, although the severity of poisoning cannot be determined from this alone and the clinical and biochemical features must be taken into account. Elimination is increased by urinary alkalinisation, which is achieved by the administration of 1.26% sodium bicarbonate.

The urine pH should be monitored, Correct metabolic acidosis with intravenous 8.4% sodium bicarbonate (first check serum potassium). Forced diuresis should not be used since it does not enhance salicylate excretion and may cause pulmonary oedema. Haemodialysis is the treatment of choice for severe poisoning and should be considered in patients with plasma salicylate concentrations >700 mg/L (5.1 mmol/L), or lower concentrations associated with severe clinical or metabolic features. Patients under 10 years or over 70 have increased risk of salicylate toxicity and may require dialysis at an earlier stage.

DOSAGE AND INSTRUCTIONS
To be sold and used on the prescription of a registered medical practitioner only. Keep out of reach of children. Do not store above 30°C. Keep in dry place. Protect from light.

PRESENTATION
Loprin 75 mg Tablets:
Alu. PVC Blister pack of 3x10's.
Loprin 150 mg Tablets:
Alu. PVC Blister pack of 3x10's.

لوپرن®
(اسپرین)

خوراک و ہدایات:
صرف مستند ڈاکٹر کے نسخہ کے مطابق ہی دوا فروخت اور استعمال کی جائے۔
بچوں کی پہنچ سے دور رکھیں۔ 30°C سے زیادہ درجہ حرارت پر نہ رکھیں۔
خشک جگہ پر رکھیں۔ روشنی سے بچائیں۔

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