SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT

Aspi-SSP 81(Acetylsalicylic Acid enteric coated Tablets BP 81 mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each enteric coated tablet contains 81mg Acetylsalicylic Acid(Aspirin) .

For the full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

White, round biconvex tablet.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Enteric Coated acetylsalicylic acid (Aspirin) 81 mg is indicated for the following uses, based on its platelet aggregation inhibitory properties:

- for reducing the risk of vascular mortality in patients with a suspected acute myocardial infarction;
- for reducing the risk of a first non-fatal myocardial infarction in individuals deemed to be at sufficient risk of such an event by their physician.
  - There is no evidence for a reduction in the risk of first fatal myocardial infarction.
  - Acetylsalicylic acid does not reduce the risk of either cardiovascular mortality or first strokes, fatal or non-fatal.
  - The decrease in the risk of first non-fatal myocardial infarction must be assessed against a much smaller but not insignificant increase in the risk of haemorrhagic stroke as well as gastrointestinal bleeding.
- for reducing the risk of morbidity and death in patients with unstable angina and in those with previous myocardial infarction;
- for reducing the risk of transient ischemic attacks (TIA) and for secondary prevention of atherothrombotic cerebral infarction.

4.2. Posology and method of administration

Recommended Dose and Dosage Adjustment

Platelet aggregation inhibitor:

Suspected Acute Myocardial Infarction: An initial dose of at least 162 mg chewed or crushed to ensure rapid absorption as soon as a myocardial infarction is suspected. The same dose should be given as maintenance over the next 30 days. After 30 days, consider further therapy based on dosage and administration for prevention of recurrent MI (see Prior Myocardial Infarction).

Prevention of a first non-fatal myocardial infarction: 81-325 mg once daily, according to the individual needs of the patient, as determined by the physician.

Prior Myocardial Infarction or Unstable Angina Pectoris: 81-325 mg daily according to the individual needs of the patient, as determined by the physician.

Transient Ischemic Attack and Secondary Prevention of Atherothrombotic Cerebral Infarction: 81-325 mg daily according to the individual needs of the patient, as determined by the physician.

Method of administration

Oral; the tablets should preferably be taken after meals, with plenty of liquid.

4.3. Contraindications

Patients who are hypersensitive to acetylsalicylic acid (Aspirin), salicylates, non-steroidal antiinflammatory drugs (NSAIDs), analgesics, antipyretics or other ingredients in the product.

-Acute gastrointestinal ulcer.

-History of gastrointestinal ulcers.

-Hemorrhagic diathesis.

-Active or Severe hepatic failure, renal failure, or congestive heart failure.

-Patients with a history of asthma induced by the administration of salicylates or substances with a similar action, notably NSAIDs

-Combination with methotrexate at doses of 15 mg/week or more.

4.4. Special warnings and precautions for use

General

Acetylsalicylic acid (Aspirin) is one of the most frequent causes of accidental poisonings in toddlers and infants. Tablets should be kept well out of the reach of children.

Aspirin should be administered cautiously to patients with:

- uncontrolled hypertension
- impaired hepatic, renal function or cardiovascular circulation (e.g. renal vascular disease, congestive heart failure, volume depletion, major surgery, sepsis or major haemorrhagic events)
- a history of bleeding tendencies, significant anemia and/or hypothrombinemia.
- concomitant treatment with anticoagulants.
- concomitant treatment with ibuprofen in patients taking low-dose Aspirin.
- concomitant treatment with NSAIDs, such as ibuprofen and naproxen in patients on an Aspirin regimen.

Hypersensitivity

Acetylsalicylic acid may precipitate bronchospasm and induce asthma attacks or other hypersensitivity reactions. Risk factors are present bronchial asthma, hay fever, nAspirinl polyps, or chronic respiratory disease. This applies also for patients showing allergic reactions (e.g. cutaneous reactions, itching, urticaria) to other substances.

Hematologic

Due to effect on platelet aggregation, acetylsalicylic acid may be associated with an

increased risk of bleeding. Caution is necessary when salicylates and anticoagulants are prescribed concurrently, as salicylates can depress the concentration of prothrombin in the plasma.

Peri-Operative Considerations

Due to its inhibitory effect on platelet aggregation which persists for several days after administration, acetylsalicylic acid may lead to an increased bleeding tendency during and after surgical operations (including minor surgeries, e.g. dental extractions).

4.5. Interaction with other medicinal products and other forms of interaction

Overview

Acetylsalicylic acid should be used with caution with other products that have anticoagulation or antiplatelet effects, as these effects may be potentiated. Drugs that bind to protein binding sites should also be used cautiously since acetylsalicylic acid may displace drugs from their protein binding site.

Contraindicated Interactions

Methotrexate, used at doses of 15 mg/week or more: Increased hematological toxicity of methotrexate (due to decreased renal clearance of methotrexate by anti-inflammatory agents in general and displacement of methotrexate from its plasma protein binding by salicylates).

Drug-Drug Interactions

Methotrexate, used at 15 mg/week or less: Salicylates may retard the elimination of methotrexate by decreasing renal clearance of methotrexate, displacing methotrexate from protein binding sites, and thereby increasing its hematological toxicity.

Anti-coagulants, thrombolytics / other inhibitors of platelet aggregation / hemostasis,

e.g. warfarin, heparin: Caution is necessary when salicylates and anticoagulants, thrombolytics / other inhibitors of platelet aggregation / hemostasis prescribed concurrently, as salicylates can depress the concentration of prothrombin in the plasma, leading to an increased risk of bleeding.

Oral hypoglycemics, e.g. insulin, sulfonylureas: Large doses of salicylates have a hypoglycemic action and may enhance the effect of oral hypoglycemic agents. Diabetics receiving concurrent salicylate and hypoglycemic therapy should be monitored closely: reduction of the sulfonylurea hypoglycemic drug dosage may be necessary.

Diuretics: Diuretics in combination with acetylsalicylic acid at higher doses leads to decreased glomerular filtration via decreased prostaglandin synthesis. As a result, sodium excretion may be decreased by salicylate administration.

Uricosuric Agents: Salicylates in large doses are uricosuric agents; smaller amounts may depress uric acid clearance and thus decrease the uricosuric effects of other drugs.

Valproic Acid: Salicylates may alter valproic acid (VPA) metabolism and may displace VPA from protein binding sites, possibly intensifying the effects of VPA. Caution is

recommended when VPA is administered concomitantly with salicylates.

Glucocorticoids (systemic), except hydrocortisone used as replacement therapy in Addison's disease: Decreased blood salicylate levels during corticosteroid treatment and risk of salicylate overdose after this treatment is stopped via increased elimination of salicylates by corticosteroids.

Angiotensin Converting Enzyme (ACE) Inhibitors: The hyponatremic and hypotensive effects of ACE inhibitors *may* be diminished by the concomitant administration of acetylsalicylic acid due to its indirect effect on the renin-angiotensin conversion pathway (i.e. inhibition of vasodilatory prostaglandins leading to decreased glomerular filtration). The potential interaction may be related to the dose of acetylsalicylic acid (3g/day or more).

Selective Serotonin Re-uptake Inhibitors (SSRIs): Increased risk of upper gastrointestinal bleeding due to possibly synergistic effect.

Digoxin: Plasma concentrations of digoxin are increased due to a decrease in renal excretion.

NSAIDS:

Aspirin and other NSAIDs: The use of other non-steroidal anti-inflammatory drugs (NSAIDs)

with salicylates at high doses (≥ 3g/day) may increase the risk of ulcers and gastrointestinal bleeding due to a synergistic effect.

Ibuprofen: Ibuprofen can interfere with the anti-platelet effect of low dose acetylsalicylic acid (81-325 mg per day). Long-term daily use of ibuprofen may render Aspirin less effective when used for cardioprotection and stroke prevention. To minimize this interaction, regular users of ibuprofen and of low-dose, immediate-release Aspirin should take the ibuprofen at least one hour after and 11 hours before the daily Aspirin dose. The use of delayed-release (e.g. enteric-coated) Aspirin is not recommended when using ibuprofen regularly.

Naproxen: Naproxen may attenuate the irreversible platelet inhibition induced by acetylsalicylic acid. Clinical pharmacodynamic data suggest that concurrent (same day) naproxen sodium usage for more than one day consecutively inhibits the effect of low-dose acetylsalicylic acid on platelet activity and this inhibition may persist for up to several days after stopping naproxen sodium therapy. The clinical relevance of this interaction is not known. Treatment with naproxen, in patients with increased cardiovascular risk may limit the cardiovascular protection of acetylsalicylic acid.

Healthcare professionals should advise consumers and patients regarding the appropriate concomitant use of NSAIDs (i.e. ibuprofen or naproxen) and Aspirin.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herb have not been established.

Drug-Laboratory Interactions

Salicylates can produce changes in thyroid function tests.

Drug-Lifestyle Interactions

Alcohol: Increased damage to gastrointestinal mucosa and prolonged bleeding time due to additive effects of acetylsalicylic acid and alcohol. Patients having 3 or more alcoholic drinks per day should consult their physician before use.

4.6. Fertility, pregnancy and lactation

Women attempting to conceive:

During the first and second trimester of pregnancy, acetylsalicylic acid containing drugs should not be given unless clearly necessary. If acetylsalicylic acid containing drugs are used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low as possible and duration of treatment as short as possible.

Pregnant Women:

Acetylsalicylic acid inhibits prostaglandin synthesis. Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies raise concern about an increased risk of miscarriage and of malformations after the use of a prostaglandin synthesis inhibitor in early pregnancy. The risk is believed to increase with dose and duration of therapy. Available data do not support any association between intake of acetylsalicylic acid and an increased risk for miscarriage. For acetylsalicylic acid the available epidemiological data regarding malformation are not consistent, but an increased risk of gastroschisis could not be excluded. A prospective study with exposure in early pregnancy (1st-4th month) of about 14,800 mother-child pairs has not yielded any association with an elevated rate of malformations.

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

-cardiopulmonary toxicity (with premature closure of the ductus ateriosus and pulmonary hypertension);

-renal dysfunction, which may progress to renal failure with oligo-hydroamniosis;

Use of any prostaglandin synthesis inhibitors at the end of pregnancy may expose the mother and the child to:

- possible prolongation of bleeding time, an anti-aggregating effect which may occur even after very low doses.
- inhibition of uterine contractions resulting in delayed or prolonged labour Consequently, acetylsalicylic acid is contraindicated in the third trimester of pregnancy.

Nursing Women:

Acetylsalicylic acid and its metabolites pass into breast milk in small quantities. Since no adverse effects on the infant have been observed after occasional use, interruption of breastfeeding is usually unnecessary. However, on regular use or on intake of high doses, breast feeding should be discontinued early.

4.7. Effects on ability to drive and use machines

Aspirin does not usually affect the ability to drive or operate machinery.

4.8. Undesirable effects

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).

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, and gingival bleeding. Symptoms may 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 digestive system disorders	*Not known*: Hyperuricemia.
Nervous system disorders	*Rare*: Intracranial haemorrhage. *Not known*: Headache, vertigo.
Ear and labyrinth disorders	*Not known*: Reduced hearing ability; tinnitus.
Vascular disorders	*Rare*: Hemorrhagic vasculitis.
Respiratory, thoracic and mediastinal disorders	*Uncommon*: Rhinitis, dyspnoea. *Rare*: Bronchospasm, asthma attacks.
Reproductive System and mammary disorders	*Rare*: Menorrhagia.
Gastrointestinal disorders	*Common*:

	Dyspepsia. *Rare*: Severe gastrointestinal haemorrhage, nausea, vomiting. *Not known*: Gastric or duodenal ulcers and perforation, diarrhoea.
Hepatobiliary disorders	*Not known*: Hepatic insufficiency.
Skin and subcutaneous tissue disorders	*Uncommon*: Urticaria. *Rare*: Steven-Johnsons syndrome, Lyells syndrome, purpura, erythema nodosum, erythema multiforme.
Renal and urinary tract disorders	*Not known*: Impaired renal function, salt and water retention.

4.9. Overdose

Although considerable inter-individual variations are involved, it can be considered that the toxic dose is about 200mg/kg in adults and 100mg/kg in children. The lethal dose of acetylsalicylic acid is 25-30 grams. Salicylate poisoning is usually associated with plasma concentrations >350 mg/L (2.5 mmol/L). Plasma concentration above 500 mg/l in adults and 300 mg/l in children generally cause sever toxicity. 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.

Overdose may harmful for elderly patients and particularly for small children (therapeutic overdose or frequent accidental intoxications may be fatal).

Symptoms of moderate intoxications:

Common features of salicylate poisoning include vomiting, nausea, abdominal pain, dehydration, tinnitus, vertigo, headache, deafness, sweating, warm extremities with bounding pulses.

Symptoms of severe intoxications:

Some degree of acid-base disturbance is present in most cases.

In the first instance hyperventilation occurs, which results in respiratory alkalosis. Respiratory acidosis ensues due to suppression of the respiratory centre.

In addition metabolic acidosis with normal or high arterial pH (normal or reduced hydrogen ion concentration) is usual in adults and children over the age of four years as a result of the presence of salicylate. In children aged four years or less, a dominant metabolic acidosis with low arterial pH (raised hydrogen ion concentration) is common. Since younger children are often not seen until they have reached a late stage of intoxication, they are usually in the stage of acidosis.

Furthermore, the following symptoms may occur: haematemesis, hyperpyrexia, hypoglycaemia, hypokalaemia, thrombocytopenia, increased INR/PTR, intravascular coagulation, renal failure

and non-cardiac pulmonary oedema, hyperthermia and perspiration, resulting in dehydration: feeling of restlessness, convulsions and hallucinations.

Central nervous system features including confusion, disorientation, convulsions may lead to coma cardiovascular collapse or respiratory arrest is less common in adults than in children.

Treatment of overdose

If a toxic dose has been ingested, hospital admission is required. In the event of moderate intoxication, including the patient to vomit should be attempted.

If this fails, gastric lavage may be attempted during the first hour after ingestion of substantial amount of the medicine.

Give activated charcoal (50g for an adult, 1g/kg body weight for a child up to 12 years) 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. Other symptoms to be treated symptomatically.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: blood and blood forming organs-antithrombotic agents: Platelet Aggregation Inhibitor excl. Heparin.

***ATC code*:** B01AC06

Aspirin inhibits platelet aggregation. Blocking the platelet cyclooxygenase by acetylation, it inhibits thromboxane A2 synthesis, a physiological activating substance released by the platelets and which would play a role in the complications of the atheromatosic lesions.

Inhibition of TXA2-synthesis is irreversible, because thrombocytes, which have no nucleus, are not capable (due to lack of protein synthesis capability) to synthesise new cyclooxygenase, which had been acetylated by acetylsalicylic acid.

The repeated doses from 20 to 325 mg involve an inhibition of the enzymatic activity from 30 to 95%. Due to the irreversible nature of the binding, the effect persists for the lifespan of a thrombocyte (7-10 days). The inhibiting effect does not exhaust during prolonged treatments and the enzymatic activity gradually begins again upon renewal of the platelets 24 to 48 hours after

treatment interruption. Acetylsalicylic acid extends bleeding time on average by approximately 50 to 100%, but individual variations can be observed.

Experimental data suggest that ibuprofen may inhibit the effect of low dose aspirin on platelet aggregation when they are dosed concomitantly. In one study, when a single dose of ibuprofen 400mg was taken within 8 hours before or within 30 minutes after immediate release aspirin dosing (81mg), a decreased effect of aspirin on the formation of thromboxane or platelet aggregation occurred. 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.

5.2. Pharmacokinetic properties

Absorption:

After oral administration, acetylsalicylic acid is rapidly absorbed from the gastrointestinal tract. However, a significant portion of the dosage is already hydrolysed to salicylic acid in the intestinal wall during the absorption process.

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 volume of distribution of acetylsalicylic acid is ca. 0.16 l/kg of body weight.

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 (75 mg –160 mg).

Excretion:

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

Core Tablet

Low substituted hydroxypropyl cellulose- BP

Hypromellose-BP

Microcrystalline cellulose PH 102-BP

Sodium dodecyl sulfate-BP

Tartaric acid-BP

Pregelatinized starch-BP

Maize starch-BP

Coating

White enteric coating premix

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

3 years

6.4. Special precautions for storage

Store below 30°C, store in a dry place.

6.5. Nature and contents of container

Clear and colourless PVC /Aluminium blisters containing tablets. 10 tablets per blister and 5 blisters in box (10x5) or 10 tablets per blister and 10 blisters in box (10x10).

6.6. Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

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8. NUMBER(S) IN THE NATIONAL REGISTER OF FINISHED PHARMACEUTICAL PRODUCTS

07042/07685/NMR/2019

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25/01/2022

10. DATE OF REVISION OF THE TEXT

25/08/2023