Prescribing information
(Summary of Product Characteristics / SPC)

1. Name of drug product

Aspirin® protect 300 mg
Enteric-coated tablet
Acetylsalicylic acid

2. Qualitative and quantitative composition

1 enteric-coated tablet contains: 300 mg acetylsalicylic acid (Ph.Eur.).
For the full list of excipients, see section 6.1.

3. Presentation

Enteric-coated tablets

4. Clinical data

4.1 Indications

Reinfarction prophylaxis.

Note:
Aspirin protect 300 mg is not foreseen for the treatment of pain.

4.2 Posology and method of administration

Posology

For reinfarction prophylaxis
A daily dose of one Aspirin protect 300 mg enteric-coated tablets (equivalent to 300 mg acetylsalicylic acid per day) is recommended.

Method of administration

The enteric-coated tablets should be taken with plenty of water, preferably at least 30 min before a meal.

Enteric-coated tablets should not be crushed, broken or chewed in order to ensure release in the alkaline environment of the intestine.

For treatment of acute myocardial infarction, the first tablet should be bitten or chewed.

Aspirin protect 300 mg is intended for long-term use. The attending doctor must decide on the length of the treatment.

4.3 Contraindications

Aspirin protect 300 mg must not be used:
- in cases of hypersensitivity to the active ingredient acetylsalicylic acid, other salicylates or any of the other ingredients listed in section 6.1
- by patients with asthma attacks in the history which were caused by salicylates or substances with a similar action, especially nonsteroidal anti-inflammatory drugs;
- by patients with acute gastrointestinal ulcers;
- by patients with haemorrhagic diathesis;
- by patients with liver- or kidney failure;
- by patients with severe heart failure for which they are not receiving adequate treatment;
- in combination with methotrexate at a weekly dosage of 15 mg or more (see section 4.5);
- in the last trimester of pregnancy at dosages above 150 mg acetylsalicylic acid/day (see section 4.6).

4.4 Warnings and other precautionary measures

Particularly careful medical supervision is required:
- in cases of hypersensitivity to other analgesic/anti-inflammatory/antirheumatic drugs or other allergenic substances (see section 4.3);
- on concomitant ingestion of some non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen and naproxen. These may weaken the anti-platelet effect of acetylsalicylic acid. Patients should be advised to talk to their physician if they are taking acetylsalicylic acid and are intending to take NSAIDs (see section 4.5).
- by patients with other allergies (e.g. with skin reactions, itching, nettle rash);
- by patients with bronchial asthma, hay fever, swelling of the nasal mucosa (nasal polyps), chronic respiratory tract diseases;
- in concomitant therapy with anticoagulant drugs;
- with a history of gastrointestinal ulcers or gastrointestinal bleeding;
- with impaired liver function;
- in patients with impaired renal function or patients with impaired cardiovascular circulation (e.g. renal vascular disease, congestive heart failure, volume depletion, major surgery, sepsis or major hemorrhagic events), since acetylsalicylic acid may further increase the risk of renal impairment and acute renal failure;
- by patients who are about to undergo surgery (including minor surgery such as dental extractions): the bleeding tendency can be increased.
- in patients suffering from severe glucose-6-phosphate dehydrogenase (G6PD) deficiency, acetylsalicylic acid may induce hemolysis or hemolytic anemia. Factors that may increase the risk of hemolysis are e.g. high dosage, fever or acute infections;

Special instructions:
At low doses acetylsalicylic acid reduces the excretion of uric acid. This may cause a gout attack in predisposed patients.

Paediatric population
Aspirin protect 300 mg should not be taken by children or adolescents with feverish illnesses unless they have been instructed to do so by a doctor and other therapeutic measures have failed. Prolonged vomiting in conjunction with such illnesses could be a sign of Reye's syndrome, a very rare but life-threatening disease which requires immediate medical attention.

Drugs containing acetylsalicylic acid should not be taken for prolonged periods or at high doses without consulting a doctor.

4.5 Interactions with other substances and other forms of interaction

Enhanced effects ranging up to an increased risk of side effects:

- Anticoagulants / Thrombolytics: Acetylsalicylic acid can increase the risk of bleeding when taken before thrombolytic treatment. Attention should therefore be paid for signs of external or internal bleeding (e.g. bruising) in patients who are scheduled to undergo thrombolytic treatment.
- Antiplatelet drugs, e.g. ticlopidine, clopidogrel: the bleeding time can be prolonged.
- Other nonsteroidal anti-inflammatory drugs and antirheumatics in general: risk for gastrointestinal ulcers and haemorrhages is increased.
- Systemic glucocorticoids (with the exception of hydrocortisone as replacement therapy for Addison's disease): increased risk for gastrointestinal side effects.
- Alcohol: elevated risk of gastrointestinal ulcers and - bleeding.
- Digoxin: elevated plasma level
- Antidiabetics: the blood glucose level can be reduced.
- Methotrexate: decrease in elimination and displacement from protein binding sites by salicylates.
- Valproic acid: displacement from protein binding sites by salicylates.
- Selective-Serotonin-Re-uptake Inhibitors (SSRIs): elevated risk of gastrointestinal bleeding due to synergistic effects.

Weakening of effects:

- Aldosterone antagonists (spironolactone and canrenoate).
- Loop diuretics (e.g. furosemide).
- Antihypertensives (especially ACE inhibitors).
- Uricosuric agents (e.g. probenecid, sulphinpyrazone).
- NSAIDs: Concomitant use (on the same day) of some NSAIDs (except acetylsalicylic acid), such as ibuprofen and naproxen, may weaken the irreversible anti-platelet effect of acetylsalicylic acid. The clinical relevance of this interaction is not known. The treatment of patients who have an elevated cardiovascular risk with some NSAIDs, such as ibuprofen or naproxen, may limit the cardioprotective effect of acetylsalicylic acid (see section 4.4).

Accordingly, patients should not take Aspirin protect 300 mg in conjunction with any of the above-mentioned substances unless expressly instructed to do so by a doctor.

4.6 Pregnancy and breast-feeding

Pregnancy

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/fœtal 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.

Previous experience with administration of ASA at daily doses of 50 to 150 mg in the second and third trimesters of pregnancy has not produced any evidence of inhibition of labour, an elevated tendency to bleed or premature closure of the ductus arteriosus.

No information is available for daily doses between 150 and 300 mg. In the last trimester of pregnancy, administration of analgesic doses of ASA may, as a result of inhibited prostaglandin synthesis, cause prolonged gestation, inhibition of labour and, from the 28th-30th week of pregnancy, premature closure of the ductus arteriosus. At these doses, there may also be an increased tendency to bleeding in both mother and child, as well as an increased incidence of intracranial haemorrhage in preterm babies if ASA is administered shortly before birth.

1st and 2nd trimester
During the first and second trimesters of pregnancy, Aspirin protect 300 mg should only be prescribed at daily doses of up to 300 mg ASA if strictly indicated.

3rd trimester
Administration of a daily dose of up to 150 mg ASA in the 3rd trimester should likewise only be prescribed if urgently indicated. In the last trimester of pregnancy, administration of Aspirin protect 300 mg at daily doses of 150 mg ASA and above is contraindicated (see section 4.3).

Breast-feeding
Small quantities of the active ingredient acetylsalicylic acid and their metabolites pass into breast milk. Detrimental effects on the infant have not been reported to date, it is therefore not necessary to interrupt breast-feeding if the daily dose does not exceed 150 mg. The infant should be weaned if higher doses are taken (more than 150 mg daily).

4.7 Effects on the ability to drive and use machines

Acetylsalicylic acid has no influence on the ability to drive and to use machines.

4.8. Undesirable effects

The following incidence rating is used to evaluate the frequency of side effects:

Very common:	≥ 1/10
Common:	≥ 1/100, < 1/10
Uncommon:	≥ 1/1,000 to, < 1/100
Rare:	≥ 1/10,000, < 1/1,000
Very rare:	< 10,000
Not known:	Frequency cannot be estimated from the available data

Blood and lymphatic system disorders:
Rare to *very rare* serious bleedings, such as cerebral bleeding, especially in patients with uncontrolled hypertension and/or concomitant treatment with anticoagulants, which in isolated cases may be potentially life-threatening, have been reported.
Hemolysis and hemolytic anemia in patients with severe forms of glucose-6-phosphate dehydrogenase (G6PD) deficiency have been reported.
Bleeding, e.g. nosebleeds, bleeding gums, cutaneous bleeding or urogenital bleedings, possibly with prolongation of the bleeding time (see section 4.4). This effect can persist for 4 to 8 days after use.

Immune system disorders:
Rare:

- Hypersensitivity reactions of the skin, respiratory tract, gastrointestinal tract and cardiovascular system, especially in asthmatics. Symptoms could be: hypotension, attacks of dyspnoea, rhinitis, nasal congestion, anaphylactic shock or angioneurotic oedema.

Metabolism and nutrition disorders:
Very rare:
- Hypoglycaemia,
- Acetyl salicylic acid at low dosage reduces uric acid excretion. This may cause a gout attack in predisposed patients.

Nervous system disorders:
Headaches, dizziness, impaired hearing ability, tinnitus and mental confusion may be signs of overdose (see section 4.9).

Gastrointestinal disorders:
Common:
- Gastrointestinal disorders such as heartburn, nausea, vomiting, abdominal pain and diarrhoea.
- Minor blood loss from the gastrointestinal tract (micro haemorrhaging)

Uncommon:
- Gastrointestinal ulcers which in very rare cases can lead to perforation.
- Gastrointestinal bleedings.
  Long-term use of Aspirin protect 300 mg may cause iron deficiency anaemia due to occult blood loss from the gastrointestinal tract.
- Gastrointestinale Entzündungen.

If you pass black stools (tarry stools) or vomit blood, both of which are a sign of serious bleeding in the stomach, you must inform your doctor immediately.

Hepatobiliary disorders:
Very rare:
- Elevated liver values.

Skin and subcutaneous tissue disorders:
Uncommon:
- Skin reactions (very rare cases ranging up to erythema exsudativum multiforme).

Renal and urinary disorders:
Very rare:
- Renal impairment and acute renal failure have been reported.

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
Bundesinstitut für Arzneimittel und Medizinprodukte
Abt. Pharmakovigilanz
Kurt-Georg-Kiesinger Allee 3
D-53175 Bonn
Website: http//www.bfarm.de

4.9 Overdose

A distinction is made between chronic acetylsalicylic acid over dosage with predominantly central nervous manifestations such as drowsiness, dizziness, confusion or nausea ("salicylism") and acute intoxication.
The cardinal feature of acute intoxication with acetylsalicylic acid is severe disruption of the acid-base balance. Even in the therapeutic dose range, respiratory alkalosis occurs as a consequence of increased respiration. This is compensated by increased renal excretion of bicarbonate, which normalises the blood's pH value. At toxic dosages, the level of compensation is no longer sufficient and both the pH value and the bicarbonate concentration in the blood drop. The plasma PCO_2 value may be temporarily normal. The apparent clinical picture is that of metabolic acidosis. However, the actual condition is a combination of respiratory and metabolic acidosis. The causes are: Respiratory restriction caused by toxic doses, acid accumulation, partially due to decreased renal excretion (sulphuric acid, phosphoric acid, salicylic acid, lactic acid, acetoacetic acid etc.) caused by impairment of carbohydrate metabolism. This is compounded by impairment of electrolyte balance. Major potassium loss occurs.

Symptoms of acute intoxication
Symptoms of milder acute intoxication (200 - 400 µg/ml):
In addition to disruption of the acid-base balance and electrolyte balance (e.g. potassium loss), hypoglycaemia, skin rashes and gastrointestinal haemorrhaging, hyperventilation, tinnitus, nausea, vomiting, disturbed vision and hearing, headache, dizziness and confusion have been observed.
With severe intoxication (above 400 µg/ml), delirium, tremor, difficult breathing, sweating, dehydration, hyperthermia and coma may occur.
In the event of intoxication with a fatal outcome, death usually occurs as a result of respiratory failure.

Treatment of intoxication
The therapeutic measures for treatment of intoxication with acetylsalicylic acid depend upon the extent, stage and clinical symptoms of the intoxication. They comprise the standard measures for decreasing absorption of the active ingredient, monitoring of the water and electrolyte balances, impaired temperature regulation and respiration.
Treatment is focused on measures to accelerate excretion and normalise the acid-base balance and the electrolyte balance. Infusion solutions of sodium hydrogen carbonate and potassium chloride and diuretics are administered. The urine reaction should be alkaline to increase the degree of salicylate ionisation and decrease the rate of back-diffusion to the tubules.
Monitoring of the blood values (pH, PCO_2, hydrogen bicarbonate, potassium, etc.) is strongly recommended. In severe cases, haemodialysis may be necessary.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antithrombotic agents, Platelet aggregation inhibitors, acetylsalicylic acid.
ATC class: B01AC06

Acetylsalicylic acid has an irreversible platelet aggregation-inhibiting action. This antiplatelet effect is achieved by acetylation of cyclooxygenase, irreversibly inhibiting the formation of thromboxane A_2 (a prostaglandin with a platelet aggregation-promoting and vasoconstrictive action) in the platelets. The effect is long-term and usually persists for the entire eight-day lifespan of a platelet.
Paradoxically, acetylsalicylic acid also inhibits the formation of prostacyclin (a prostaglandin with platelet aggregation-inhibiting but vasodilating effects) in the endothelial cells of the vascular walls. This effect is transient.
Once the acetylsalicylic acid has been washed out of the blood, the nucleated endothelial cells resume their production of prostacyclin.
As a consequence, once daily administration of low-dosage (< 300 mg / day) acetylsalicylic acid causes inhibition of thromboxane A_2 in the platelets without markedly impairing prostacyclin formation.
Acetylsalicylic acid also belongs to the class of acid-forming nonsteroidal anti-inflammatory drugs with analgesic, antipyretic and anti-inflammatory properties. Its mechanism of action is based on irreversible inhibition of cyclooxygenase enzymes involved in prostaglandin synthesis.
Acetylsalicylic acid is used at higher oral doses to treat mild to moderate pain, elevated temperature and acute and chronic inflammatory diseases (e.g. rheumatoid arthritis).

Experimental data suggest that ibuprofen may inhibit the effect of low dose acetylsalicylic acid on platelet aggregation when they are dosed concomitantly. In one study, when a single dose of ibuprofen 400 mg was taken within 8 h before or within 30 min after immediate release aspirin dosing (81 mg), a decreased effect of ASA 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 clinical situation imply that no firm conclusion 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

Acetylsalicylic acid is converted before, during and after absorption into its main metabolite salicylic acid. The metabolites are excreted primarily via the renal route.
In addition to salicylic acid, the main metabolites of acetylsalicylic acid are the glycine conjugate of salicylic acid (salicyluric acid), the ether and ester glucuronides of salicylic acid (salicyl phenylglucuronide and salicyl acetylglucuronide) and gentisic acid, produced by oxidation of salicylic acid, and its glycine conjugate.
Depending on the formulation, absorption of acetylsalicylic acid following oral administration is rapid and complete. The residual acetyl portion of acetylsalicylic acid undergoes partial hydrolytic cleavage during its passage through the mucous membranes oft the gastrointestinal tract.
Peak plasma concentrations are attained after 10-20 min (acetylsalicylic acid) and 0.3-2 h (total salicylate).
The elimination kinetic of salicylic acid is dependent to a great extent on the dose, as the capacity for metabolisation of salicylic acid is limited (elimination half-life fluctuates between 2 and 30 h).
The elimination half-life of acetylsalicylic acid is only a few minutes; the elimination half-life of salicylic acid is 2 h after consumption of a dose of 0.5 g acetylsalicylic acid and 4 h after administration of 1 g; following consumption of a single dose of 5 g, the elimination half-life is extended to 20 h.

Protein binding in human plasma is dependent on the concentration; values ranging from 49 % to over 70 % (acetylsalicylic acid) and 66 % to 98 % (salicylic acid) have been reported.
Salicylic acid has been detected in cerebrospinal fluid and synovial fluid after consumption of acetylsalicylic acid.
Salicylic acid crosses the placental barrier and passes into breast milk.

5.3 Preclinical safety data

The preclinical safety profile of acetylsalicylic acid is well documented. In animal tests salicylates caused kidney damage and gastrointestinal ulcers.
Acetylsalicylic acid has been appropriately tested for mutagenicity and carcinogenicity; no relevant evidence of a mutagenic or carcinogenic potential was found.
Salicylates have shown teratogenic effects in a number of animal species. There have been implantation disturbance, embryotoxic and fetotoxic effects, and learning disorders in the young animals after prenatal exposure.

6. Pharmaceutical data

6.1 Other ingredients

Maize starch
Cellulose powder
Methacrylic acid – ethylacrylate copolymer 1:1 dispersion 30%
Polysorbat 80
Sodium Dodecylsulfate
Talc
Triethyl citrate

6.2 Incompatibilities

None

6.3 Shelf-life

5 years.

6.4 Special storage instructions

Do not store at temperatures above 25°C.

6.5 Type and contents of container

PP aluminium blisters:
Packs of 42 and 98 enteric-coated tablets;
Not all pack sizes may be marketed.

6.6 Instructions for use

None

7. Product license holder

Bayer Vital GmbH,
51368 Leverkusen
Germany

8. Registration number

16854.00.01, 30828.00.01, 33171.01.00

9. Date of registration/extension of registration

16854.00.01: 28.12.1993 / 12.09.2007
30828.00.01: 28.12.1993 / 25.07.2007
33171.01.00: 09.10.1995 / 18.11.2013

10. Date of preparation

03.2017

11. Prescription/pharmacy status

Pharmacy only