SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Acetylsalicylic acid Bluefish 75 mg tablets
Acetylsalicylic acid Bluefish 160 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 75 mg acetylsalicylic acid.
Each tablet contains 160 mg acetylsalicylic acid.

For the full list of exipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.

75 mg: White to off-white, clear to mottled, 6.5 mm round, biconvex, uncoated tablets plain on both sides.

160 mg: White to off-white, clear to mottled, 8.5 mm round, biconvex, uncoated tablets with break line on one side and plain on other side. The score line is only for ease of swallowing and not to divide into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Acute myocardial infarction, Prophylaxis of cardiovascular complications after acute myocardial infarction and in unstable coronary syndromes (unstable angina pectoris, completed non-Q-wave myocardial infarction) and stable angina pectoris.

Secondary prophylaxis against recurrence of cerebrovascular disease as TIA (transient ischemic attacks) and RIND (reversible ischemic neurological defect).

4.2 Posology and method of administration

Posology
Acute myocardial infarction: Initially given a loading dose of 150-500 mg. The loading dose is given as soon as possible after onset of symptom.

Prophylaxis of cardiovascular complications after acute myocardial infarction, unstable coronary syndrome (unstable angina pectoris, completing non-Q-wave myocardial infarction), stable angina pectoris: 1 tablet of 75 mg per day.

Prophylaxis of recurrence of cerebrovascular disease: 1 tablet of 75 mg per day.

Method of administration
For oral use.
4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Due to cross-reaction the product should not be given to patients who have experienced symptoms of asthma, rhinitis or urticaria after taking acetylsalicylic acid or other anti-inflammatory agents of non-steroidal type.
- Hemophilia.
- Thrombocytopenia.
- Active, or history of recurrent peptic ulcer and/or gastric/intestinal haemorrhage.
- Liver cirrhosis.
- Severe heart failure.
- Doses > 100 mg / day during the third trimester of pregnancy.

4.4 Special warnings and precautions for use

Acetylsalicylic acid Bluefish is used in the following cases only after careful consideration of risks and benefits:

- In concomitant treatment with anticoagulation (coumarin derivatives or heparin - except low dose therapy with heparin).
- For treatment of patients with gastrointestinal diseases.
- For treatment of patients with severe renal disease (glomerular filtration rate below 30 mL / min).
- For treatment of patients with mild to moderate heart failure, kidney or liver disease, particularly with a concomitant diuretic treatment, the risk of fluid retention and impaired renal function must be taken into account.
- For patients with bronchial asthma, chronic obstructive lung diseases, hay fever or nasal polyps. These patients are at increased risk of hypersensitivity reactions when taking analgesics, non-steroidal type (NSAIDs) with asthmatic attack, angioedema or urticaria.
- Acetylsalicylic acid Bluefish may increase the risk of gastrointestinal bleeding with concomitant intake of alcohol.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions

Anticoagulants, thrombolytics / other inhibitors of platelet aggregation:
Salicylates inhibit the platelet function and therefore strengthening the anticoagulants effect. Due to the increased risk of bleeding, care should be exercised in combination treatment. Monitoring of coagulation is recommended.

Cyclosporine, tacrolimus:
Co-administration of NSAIDs and cyclosporine or tacrolimus may increase the nephrotoxic effect of cyclosporine and tacrolimus. The renal function should be monitored when NSAIDs and any of these medicines are combined.

Diuretic and antihypertensive
NSAIDs may reduce the effect of diuretics and antihypertensive drugs. As with other NSAIDs, the risk of acute renal failure may increase when ACE inhibitors are combined with acetylsalicylic acid.
Corticosteroids and non-steroidal anti-inflammatory drugs, NSAIDs
The combination of acetylsalicylic acid and corticosteroids or other NSAIDs may cause an increased risk of gastrointestinal bleeding.

Agents that increase the excretion of uric acid:
Salicylates counteracts the effect of probenecid and the combination should be avoided.

Ibuprofen:
Experimental data suggest that ibuprofen may inhibit the effect of low dose acetylsalicylic acid has on thrombocyte aggregation when given simultaneously. 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).

Pharmacokinetic interactions
Methotrexate:
Acetylsalicylic acid and other NSAIDs inhibit the tubular secretion of methotrexate. The combination is therefore increasing plasma concentrations of methotrexate. This increases the risk of side effects of methotrexate, which is particularly serious at high (oncology) doses. Combined with high-dose methotrexate should therefore be avoided. Studies of acetylsalicylic acid and a low dose of methotrexate shows that acetylsalicylic acid significantly increase the levels of the potentially cytotoxic metabolite 7-OH-methotrexate in plasma.

Digoxin and lithium:
Acetylsalicylic acid inhibits the renal excretion of digoxin and lithium, with elevated plasma concentrations of the agents as a result. The determination of the plasma concentration of digoxin and lithium is recommended at initiation and withdrawal of acetylsalicylic acid. A dose adjustment may be required.

Valproic acid:
Acetylsalicylic acid has been reported to decrease the binding of valproate to serum albumin and thereby increase its free plasma concentration levels at steady state.

Phenytoin:
Salicylate reduces the binding of phenytoin to plasma albumin. This may lead to lower concentrations of total phenytoin in plasma but an increase in the free fraction of phenytoin. The unbound plasma concentration, and thus the therapeutic effect does not appear to be significantly affected.

Sulfonylureas:
Salicylic is considered to be able to potentiate the hypoglycemic effect of sulphonyl urea. A series of case reports speak for this. The mechanism is unclear, but may involve a decreased binding of the sulfonylureas to serum albumin in contrast to this the total serum concentrations of glibenclamide has been observed to decrease and oral clearance increased by concomitant administration of acetylsalicylic acid.

Nicotinic acid.
For administration of acetylsalicylic acid (1 g), the plasma levels of nicotine acid substantially increased in an experimental study. The mechanism includes likely the glycine competitive inhibition of nicotinic acid.

4.6 Fertility, pregnancy and lactation

Pregnancy

Low doses (up to 100 mg / day)
Clinical studies indicate that doses up to 100 mg / day, which require specialized monitoring, appear safe.

Doses of 100 mg - 500 mg / day
There is insufficient clinical experience for doses between 100 mg / day and 500 mg / day. Thus, the recommendation below is also for this dose range.

Doses of 500 mg / day and higher
Inhibition of prostaglandin synthesis may affect the pregnancy in a negative way. Data from epidemiological studies suggest an increased risk of miscarriage and risk 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% to about 1.5%. The risk is believed to increase with higher dose and the duration of therapy. In animals, the administration of prostaglandin synthesis inhibitors has been shown to result in increased pre- and post-implantation losses and embryo / fetal death. Increased incidences of various malformations, including cardiovascular, have been reported in animals exposed to a prostaglandin synthesis inhibitor during the period of organogenesis. During the first and second trimester of pregnancy, should acetylsalicylic acid be used only when absolutely necessary. If acetylsalicylic acid is used by a woman trying to become pregnant, or are given during the first and second trimester of pregnancy, the dose should be as low and duration of treatment as short as possible.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the fetus to:
- Cardiopulmonary toxicity (premature closure of the ductus arteriosus and pulmonary hypertension).
- Renal dysfunction, which can lead to renal failure and thereby a reduced quantity of amniotic fluid.

At the end of pregnancy, all prostaglandin synthesis inhibitors may expose the mother and the fetus to:
- Bleeding, an anti-aggregation effect of platelets that can occur even at very low doses.
- Inhibition of uterine contractions resulting in delayed / prolonged labor.

The above implies that acetylsalicylic acid in doses greater than 100 mg / day is contraindicated during the third trimester of pregnancy.

Breast-feeding

Low quantities of salicylates and their metabolites are excreted in the breast milk. Short term use of therapeutic doses does not require interruption of breastfeeding since no side effects for nursing infants have been reported. For long-term use and / or treatment with high doses the breastfeeding should be discontinued.
Fertility
Treatment with Acetylsalicylic acid Bluefish can lead to reduced fertility in women and is not recommended for women attempting to conceive. Discontinuation of the drug should be considered in women who have difficulty conceiving or who are undergoing fertility investigation.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The most common side effect is dyspeptic symptoms, approximately 2-6%. The increased risk of haemorrhage, especially from the gastrointestinal tract, is rarely symptomatic.

Adverse reactions are listed below by system organ class and frequency.
Common (≥1/100 to <1/10)

Blood and lymphatic system disorders: increased bleeding.
Gastrointestinal disorders: Dyspepsia.

Uncommon (≥1/1,000 to <1/100)

General: Allergic reactions (urticaria, rhinitis, asthma).

Rare (≥1/10,000 to <1/1,000)

Gastrointestinal disorders: Severe gastrointestinal bleeding.
Nervous system disorders: Intracranial bleeding.
Skin and subcutaneous tissue disorders: Severe skin reactions.
Renal and urinary tract disorders: Renal disorders.

People with known allergy or asthma are at increased risk of hypersensitivity reactions. Less blood loss may in rare cases lead to anemia. Severe gastrointestinal bleeding occurs only at higher doses and at regular use.

Dizziness and tinnitus can be symptoms of overdose, especially in children and the elderly.

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 the national reporting system listed in Appendix V.*

4.9 Overdose

Toxicity
Children under 3 years are particularly susceptible. 150 mg / kg brings relief, 150-300
mg / kg of mild-moderate and more than 300 mg / kg severe intoxication. The level of salicylate in blood is valuable for the assessment but must always be related to the time factor and the clinical picture. (More than 2.5 mmol / l may bring relief, 3.5-4.5 mmol / l moderate, 4.5-6.0 mmol / l serious and > 6.0 mmol / l in extremely severe intoxication; note that this applies approximate initial values, later on relatively low salicylate value can be presented at severe intoxication.) 0.9-5 g to 3 months-3 year olds gave moderate-severe intoxication. 10-25 g to 14-15 year olds gave after gastric lavage mild-moderate intoxication. Severe hypersensitivity reactions may occur especially in children during the first six months of life. Poisoning can also occur by absorption through the skin following repeated administration (psoriasis and ichthyosis patients).

**Symptoms**

**Treatment**
If necessary gastric lavage. Repeated doses of charcoal (shortens the half-life considerably). S- salicylate should be determined. Rehydration, correction of metabolic acidosis and any electrolyte disturbances. Omeprazole is to protect the stomach lining. Antiemetic e.g. ondansetron when needed. (in order to provide carbon repeatedly at frequent vomiting.) Alkalinity of the urine with sodium bicarbonate (sodium bicarbonate) i.v. for accelerated elimination. Add glucose. Follow the coagulation status. Vitamin K is given in case of mass poisoning or coagulation disorder. When bleeding complication platelet concentrate is given and / or fresh frozen plasma. At insufficient efficacy fibrinolysis is given in consultation with coagulation expert. Respiratory therapy of unconsciousness or severe general effect. In severe poisoning (high salicylate value or moderate value in combination with pronounced acidosis and CNS disorder), as well as in renal failure, hemodialysis should be considered. Symptomatic therapy (regarding e.g. hyperthermia, cerebral edema, pulmonary edema).

5. **PHARMACOLOGICAL PROPERTIES**

5.1 **Pharmacodynamic properties**

Pharmacotherapeutic group: Platelet aggregation inhibitors, ATC code: B01AC06

Acetylsalicylic acid has an inhibitory effect on the platelet aggregation. Although the mechanism is not fully understood, the effect appears primarily be exerted through acetylation and therefore irreversible inactivation of the enzyme cyclooxygenase, which is involved in the formation of thromboxane A2 in platelets and of prostacyclin in the endothelium. These are basically the antagonists on platelet aggregation and vascular effects. The effect on platelets are permanent, since they lack the ability to regenerate cyclooxygenase. The effect persists therefore throughout the platelet life cycle, which is 7-10 days. The prophylactic and therapeutic use in the arterial thromboembolism is based on this effect. Acetylsalicylic acid inhibits the renal prostacyclin synthesis. In
patients with normal renal function, this effect is not significant. In patients with chronic renal insufficiency, cardiac or hepatic impairment or state with reduced plasma volume the inhibited prostacyclin synthesis may lead to acute renal insufficiency, fluid retention and heart failure. See section 4.3.

Experimental data suggest that ibuprofen may inhibit the effect that low dose acetylsalicylic acid has on the platelet aggregation when given simultaneously. In one study, when a single dose of ibuprofen 400 mg either was taken within 8 hours before or within 30 minutes after intake of acetylsalicylic acid (81 mg), a decreased effect of acetylsalicylic acid was shown on the formation of thromboxane or the platelet aggregation.

Limitations of these data and the uncertainties regarding extrapolation of \textit{ex vivo} data to the clinical situation imply that no firm conclusion can be made for regular use of ibuprofen, and no effect of clinical significance are considered likely for occasional use of ibuprofen.

5.2 Pharmacokinetic properties

The absorption of acetylsalicylic acid occurs primarily in the small intestine but also in the ventricle. Maximum plasma concentrations are reached within 40 minutes. Acetylsalicylic acid is hydrolyzed with a half-life of 30 minutes to salicylic acid, which in therapeutic dose to about 80\% is bound to albumin. The elimination of salicylic acid is dose-dependent. At daily doses less than 3 g of the half-life 2-4 hours. Salicylic acid and its metabolites are substantially excreted by the kidneys. Magnesium oxide is added to accelerate the acetylsalicylic acid dissolution in the gastrointestinal tract.

5.3 Preclinical safety data

No data available

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Magnesium oxide
Cellulose microcrystalline
Maize starch
Gelatin
Silica, colloidal anhydrous
Talc
Stearic acid

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

21 months
6.4 **Special precautions for storage**

Do not store above 25°C.
Store in the original package in order to protect from moisture.

6.5 **Nature and contents of container**

The 75 mg and 160 mg tablets are packed in HDPE bottles with a polypropylene (PP) screw cap and silica gel desiccant.

75 mg: 50, 100, 105 and 500 tablets
160 mg: 50, 100 and 105 tablets

Not all pack sizes may be marketed.

6.6 **Special precautions for disposal and other handling**

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. **MARKETING AUTHORISATION HOLDER**

[To be completed nationally]

8. **MARKETING AUTHORISATION NUMBERS**

[To be completed nationally]

9. **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

[To be completed nationally]

10. **DATE OF REVISION OF THE TEXT**

2017-10-19