SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE FINISHED PHARMACEUTICALPRODUCT

Aspirem 75 mg gastro-resistant tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 75 mg aspirin.

Excipient(s) with known effect
This product contains 37.1 mg lactose and 1.9 mg sucrose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Gastro-resistant tablet.

White, round, enteric-coated tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Aspirin has an antithrombotic action, mediated through inhibition of platelet activation, which has been shown to be useful in secondary prophylaxis following myocardial infarction and in patients with unstable angina or ischaemic stroke.

Aspirem is indicated when prolonged dosage of aspirin is required. The special coating resists dissolution in gastric juice, but will dissolve readily in the relatively less acid environment of the duodenum. Owing to the delay that the coating imposes on the release of the active ingredient, Aspirem is unsuitable for the short-term relief of pain.

4.2 Posology and method of administration

Aspirem is for oral administration to adults only.

Posology

Antithrombotic action: The usual dose is 75 mg, daily. When rapid apsorption is required (e.g., following acute myocardial infarction), two tablets(150 mg)should be taken together and chewed.

The elderly: As for adults.
In general, aspirin should be used with particular caution in elderly patients who are more prone to adverse events. Undesirable effects may be minimised by using the lowest effective

dose for the shortest duration necessary to control symptoms (see section 4.4). Treatment should be reviewed at regular intervals.

Children: do not give to children and adolescents aged under 16 years, except on medical advice, where the benefit outweighs the risk (see section 4.4).

Method of administration
Oral administration.

4.3 Contraindications

Hypersensitivity to aspirin (e.g. bronchospasm, rhinitis, urticaria), to non-steroidal anti-inflammatory drugs orto any of the excipients listed in Section 6.1.

Hypoprothrombinaemia, haemophilia cerebral haemorrhage and active peptic ulceration.

History of gastrointestinalbleeding or perforation, related to previous NSAIDs therapy. Active, or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding).

Severe heart failure.

4.4 Special warnings and precautions for use

Undesirable effects associated with non-steroidal anti-inflammatory drugs (NSAIDs) may be reduced by using the minimum effective dose for the shortest possible duration. Patients treated with NSAIDs long-term should undergo regular medical supervision to monitor for adverse events.

The use of Aspirem with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided.

Gastrointestinal bleeding, ulceration and perforation: GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at anytime during treatment, with or without warning symptoms or a previous history of serious GI events.

The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (see section 4.3), and in the elderly. These patients should commence treatment on the lowest dose available. Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low dose aspirin, or other drugs likely to increase gastrointestinal risk (see below and 4.5).

Patients with a history of GI toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially GI bleeding) particularly in the initial stages of treatment.

Caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as

warfarin or selective serotonin-reuptake inhibitors or antiplatelet agents such as clopidogrel and dipyridamole (see section 4.5).

When GI bleeding or ulceration occurs in patients receiving Aspirem, the treatment should be withdrawn.

NSAIDs should be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) as their condition may be exacerbated (see section 4.8 – undesirable effects).

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 and adolescents aged under 16 years unless specifically indicated.

Aspirin can reduce uric acid excretions and so should be used with care in patients with gout or a history of gout.

Aspirin should be used with caution in patients with impaired renal, cardiac or hepatic function (avoid if severe), or in patients who are dehydrated since the use of NSAIDs may result in deterioration of renal function. Assessment of renal function should occur prior to the initiation of therapy and regularly thereafter.
Aspirin should be used with caution in patients with a history of peptic ulceration, inflammatory bowel disease or coagulation abnormalities. They may also induce gastro-intestinal haemorrhage, occasionally major.

Elderly patients are particularly susceptible to the adverse effects of NSAIDs, including aspirin especially gastrointestinal bleeding and perforation which may be fatal (see section 4.2). Where prolonged therapy is required, patients should be reviewed regularly.

In patients with strokes, aspirin should not be given until the possibility of cerebral haemorrhage has been excluded.

Aspirin may also precipitate bronchospasm or induce attacks of asthma in susceptible subjects.

Aspirin decreases platelet adhesiveness and increases bleeding time. Haematological and haemorrhagic effects can occur, and may be severe. Patients should report any unusual bleeding symptoms to their physician.

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs (see section 4.8). Patients appear to be at highest risk of these reactions early in the course of therapy, the onset of the reaction occurring in the majority of cases within the first month of treatment. Aspirem should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Cardiovascular and cerebrovascular effects

Appropriate monitoring and advice are required for patients with a history of hypertension and/or mild to moderate congestive heart failure as fluid retention and oedema have been reported in association with NSAID therapy.

Care should be taken when stopping therapy in those patients with multiple risk factors as the risk of a cerebrovascular event in the four weeks after aspirin discontinuation is significant. The risk/benefit of stopping aspirin therapy in the case of patients undergoing surgery should be considered.

Aspirem 75 mg gastro-resistant tablets contains lactose
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Aspirem 75 mg gastro-resistant tablets contains sucrose
Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Aspirin may enhance the effect of anticoagulants, antiplateletagentsand fibrinolytics leading to increased risk of bleeding.

Concomitant use of alcohol with aspirin may increase the risk of gastrointestinal bleeding.

It is considered unsafe to take NSAIDs in combination with warfarin or heparin unless under direct medical supervision.

Salicylatesinhibit the uricosuric effect of uricosuric drugs.
Care should be taken in patients treated with any of the following drugs as interactions have been reported:

Anti-coagulants: NSAIDs may enhance the effects of anti-coagulants, such as warfarin (see section 4.4).

Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs): increased risk of gastrointestinal bleeding (see section 4.4).

Anti-hypertensives: reduced anti-hypertensive effect.

Diuretics: reduced diuretic effect. Diuretics can increase the risk of nephrotoxicity of NSAIDs.

Cardiac glycosides: NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma cardiac glycoside levels.

Lithium: decreased elimination of lithium.

Methotrexate: decreased elimination of methotrexate.

Cyclosporin: increased risk of nephrotoxicity with NSAIDs.

Gold: risk of increased hepatotoxicity with aspirin.

Aminoglycosides: reduction in renal function in susceptible individuals, decreased elimination of aminoglycoside and increased plasma concentrations.

Probenecid: reduction in metabolism and elimination of NSAIDs and metabolites.

Thiopental: Aspirin may potentiate the effects of thiopental anaesthesia.

Oral hypoglycemic agents: inhibition of metabolism of sulfonylurea drugs, prolonged half-life and increased risk of hypoglycaemia.

Antacids: Patients using gastro-resistant aspirin should be advised against ingesting antacids simultaneously, to avoid premature drug release.

Corticosteroids: Plasma salicylate concentrations may be reduced by concurrent use of corticosteroids, and salicylate toxicity may occur following withdrawal of the corticosteroids. The risk of gastrointestinal ulceration and bleeding may be increased when aspirin and corticosteroids are co-administered (see Section 4.4).

Carbonic anhydrase inhibitors: Concurrent administration of carbonic anhydrase inhibitors such as acetazolamide and salicylates may result in severe acidosis and increased central nervous system toxicity.

Other NSAIDs: Avoid concomitant use with other NSAIDs.

Ibuprofen: 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 use (see section 5.1).

Phenytoin and valproate: The effect of phenytoin and valproate may be enhanced by aspirin. However, no special precautions are needed.

Aspirin can interfere, to varying degrees, with some urine tests for catecholamines, dopa, glucose, ketones, hippuric acid, homogentisic acid, homovallinic acid, 17-hydroxycorticosteroids, 5-hydroxyindoleacetic acid, urine pregnancy tests and with some serum or plasma tests for albumin, barbiturates, calcium, propylthiouracil, tyrosine and uric acid.

4.6 Fertility, pregnancy and lactation

Pregnancy

Caution should be exercised when considering use in pregnant patients. Aspirin has the ability to alter platelet function and there may be a risk of haemorrhage in infants whose mothers have consumed aspirin during pregnancy. Prolonged pregnancy and labour, with increased

bleeding before and after delivery, decreased birth weight and increased rate of stillbirth have been reported with high blood salicylate levels. With high doses there may be premature closure of the ductus arteriosus and possible kernicterus or persistent pulmonary hypertension in the newborn. Analgesic doses of aspirin should be avoided during the last trimester of pregnancy.

Numerous malformations have been reported following maternal use of aspirin during pregnancy, however with the exception of a possible risk of gastroschisis, no specific pattern of malformations has been observed and a causative role for aspirin has not been proven.

Lactation
As aspirin is secreted in breast milk, Aspirem should not be taken by patients who are breast-feeding, as there is a risk of Reye's syndrome in the infant. High maternal doses may impair platelet function in the infant.

Fertility
Women attempting to conceive should not use any NSAID, including aspirin, because of the findings in a variety of animal models that indicate these agents block blastocyst implantation.

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

4.8.1 Summary of the safety profile
The most commonly observed adverse events are gastrointestinal in nature.

4.8.2 Tabulated list of adverse reactions
Undesirable effects are listed by MedDRA System Organ Classes.
Assessment of undesirable effects is based on the following frequency groupings:
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
Not known: cannot be estimated from the available data

System Organ Class	**Undesirable Effect**
Blood and lymphatic system disorders	*Not Known:* Bleeding disorders Anaemia[1] Thrombocytopenia
Immune system disorders	*Not Known:* Hypersensitivity reactionsincluding skin rashes,urticaria, angioedema, asthma,bronchospasm and anaphylaxis. Bullous reactions includingStevens-Johnson and toxicepidermal necrolysis syndrome

Nervous system disorders	*Not Known:* Cerebral haemorrhage
Ear and labyrinth disorders	*Not Known:* Tinnitus
Cardiac disorders	*Not Known:* Cardiac failure
Vascular disorders	*Not Known:* Hypertension Haemorrhages[2] Haematoma[2]
Respiratory thoracic and mediastinal disorders	*Not Known:* Epistaxis Haemoptysis
Gastrointestinal disorders[3]	*Not Known:* Peptic ulcers[4] GI Perforation[4] GI Bleeding[4] Nausea Vomiting Diarrhoea Flatulence Constipation Dyspepsia Abdominal pain Melaena Haematemesis Ulcerative stomatitis Exacerbation of colitis Exacerbation of Crohn's disease Gastritis Gastrointestinal ulcer
Skin and subcutaneous tissue disorders	*Not Known:* Purpura Ecchymoses
Renal and urinary disorders	*Not Known:* Haematuria Urate kidney stones
General disorders and administration site disorders	*Not Known:* Oedema
Investigations	*Not Known:* Bleeding time prolonged

[1]May occur following chronic GI blood loss or acute haemorrhage.
[2]May occur in various organ systems and may be fatal.
[3]The special coating of Nu-Seals helps to reduce the incidence of side effects resulting from gastric irritation.
[4]Sometimes fatal, particularly in 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.

4.9 Overdose

If overdosage is suspected, the patient should be kept under observation for at least 24 hours, as symptoms and salicylate blood levels may not become apparent for several hours. With the gastro-resistant formulation, peak plasma levels may not occur for up to 12 hours.

Symptoms
Common features 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.

Uncommon features include haematemesis, hyperpyrexia, hypoglycaemia, hypokalaemia, thrombocytopenia, increased INR/PTR, intravascular coagulation, renal failure and non-cardiogenic pulmonary oedema.

Central nervous system features including confusion, disorientation, coma and convulsions are less common in adults than in children.
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.

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.

Management
Give oral activated charcoal if an adult presents within one hour of ingestion of more than 125 mg/kg. The plasma salicylate concentration should be measured for patients who have ingested >125 mg/kg. However, the severity of poisoning cannot be determined from this alone and the clinical and biochemical features must be taken into account.

Urea and electrolytes, INR/PTR and blood glucose should be monitored. Elimination is increased by urinary alkalisation, which is achieved by the administration of intravenous sodium bicarbonate. The urine pH should be monitored and further intravenous sodium bicarbonate may be required to maintain urinary pH 7.5-8.5 (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

and over 70 have increased risk of salicylate toxicity, and may require dialysis at an earlier stage.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antithrombotic agents,ATC code:B01AC06

Aspirin has an antithrombotic action which is mediated through inhibition of platelet activation.

Aspirem tablets have a gastro-resistant coat sandwiched between a sealing coat and a top coat. The gastro-resistant coat is intended to resist gastric fluid whilst allowing disintegration in the intestinal fluid.

Owing to the delay that the coating imposes on the release of the active ingredient, Aspirem is unsuitable for the short-term relief of pain.
Experimental data suggest that ibuprofen may inhibit the effect of low aspirin on platelet aggregation when they are dosed concomitantly.In one study, when a single dose of ibuprofen 400 mg was taken within 8h before or within30min after immediate release aspirin dosing (81 mg), a decreased effect of aspirinon 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

In a bioequivalence study comparing the pharmacokinetics of the 300 mg product with 4 x 75 mg presentation in human volunteers, measures such as terminal phase half-life, area-under-the curve and peak plasma concentrations were recorded on days 1 and 4. On day 1 salicylate reached a peak plasma concentration of between 10.34 and 31.57 mcg/ml and between 11.76 and 27.47 mcg/ml for the 300 mg and 75 mg tablets respectively. Time to peak concentration ranged from 4 to 8 hours and from 3 to 6 hours respectively. AUC ranged from 54.0 to 131.2 and from 64.3 to 137.6 h.mcg/ml respectively. The terminal phase half-life ranged from 1.33 to 2.63 hours and from 1.47 to 2.59 hours respectively. On day 4, C_{max} varied from 15.01 to 48.97 mcg/ml for the 300 mg tablet and from 11.26 to 60.21 mcg/ml for 4 x 75 mg tablets. T_{max} ranged from 4 to 8 hours and from 3 to 8 hours, whilst AUC ranged from 89.8 to 297.4 h.mcg/ml and from 61.5 to 293.4 h.mcg/ml respectively.

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the Summary of Product Characteristics.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core
Lactose monohydrate
Maize starch
Sucrose
Talc

Coating
Polyacrylate dispersion 30 per cent
Polyethylene glycol 6000
Talc
Hypromellose
Titanium Dioxide E171

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store below 25 ºC.Protect from light and moisture.

6.5 Nature and contents of container

PVC-PVDC/Aluminium blisters. Pack-sizes of 28, 50 and 56 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Remedica Ltd
Aharnon Str., Limassol Industrial Estate,
3056 Limassol, Cyprus

8. MARKETING AUTHORISATION NUMBER(S)

07940/08476/REN/2022

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of latest renewal: 14-07-2021

10. DATE OF REVISION OF THE TEXT

04/07/2023