# Summary of Product Characteristics

## 1. NAME OF THE MEDICINAL PRODUCT

ASPESINE 300 mg/250 mg/30 mg, tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One tablet contains 300 mg of acetylsalicylic acid (aspirin), 250 mg of paracetamol and 30 mg of caffeine.

Administration mode:
Oral route.

Excipient(s) with known effect
Methyl p-hydroxybenzoate (E 218), Propyl p-hydroxybenzoate (E 216).
For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

White and pink oblong tablets, with a score line on one side.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

ASPESINE is indicated in adults for the acute treatment of headache and migraine attacks with or without an aura.

### 4.2 Posology and method of administration

Posology

Adults (18 years and older)

**For headaches:**
The usual recommended dosage is 1 tablet; an additional tablet can be taken, with 4 to 6 hours between doses. In case of more intense pain, it is possible to take 2 tablets. If needed, an additional 2 tablets can be taken, with 4 to 6 hours between doses. ASPESINE is intended for episodic use, up to 4 days for headache.

**For migraine:**
Take 2 tablets when symptoms appear. If needed an additional 2 tablets can be taken, with 4 to 6 hours between doses.

ASPESINE is intended for episodic use, up to 3 days for migraine

For both headache and migraine, intake must be limited to 6 tablets in 24 hours. The medicinal product must not be used for a longer period or at higher dosage without first consulting a doctor.

Drink a full glass of water with each dose.

Children and adolescents (under 18 years of age):
The safety and efficacy of ASPESINE have not been assessed in children and adolescents. The use of ASPESINE is therefore not recommended in children and adolescents (see section 4.4).

Elderly patients:
Based on general medical considerations, caution should be exercised in elderly patients, in particular in elderly patients with a low body weight.

Hepatic and renal impairment:
The effect of hepatic or renal disease on the pharmacokinetics of ASPESINE has not been evaluated. Due to the mechanism of action of acetylsalicylic acid (aspirin) and paracetamol, this could enhance the renal or hepatic impairment. Thus, ASPESINE is contra-indicated in patients with severe hepatic or renal failure (e.g. GFR <30mL/min/1,73m²) (see section 4.3), and should be used with caution in patients with mild to moderate hepatic or renal impairment (e.g. (GFR >30mL/min/1,73m²) (see section 4.4).

## 4.3 Contraindications

- Hypersensitivity to acetylsalicylic acid (aspirin), paracetamol, caffein or to any of the excipients listed in section 6.1.
- Patiens in whom attacks of asthma, bronchospasm, angioedema, urticaria or acute rhinitis are precipitated by acetylsalicylic acid (aspirin) or other non-steroidal anti-inflammatory drugs such as diclofenac or ibuprofen.
- Active gastric or intestinal ulcer, gastrointestinal bleeding or perforation and in patients with a history of peptic ulceration.
- Haemophilia or other haemorragic disorders.
- Severe hepatic or renal impairment or failure (GFR >30mL/min/1,73m²).
- Severe cardiac failure.
- Intake of more than 15 mg of methotrexate per week (see section 4.5).
- Last trimester of pregancy (see section 4.6).

## 4.4 Special warnings and precautions for use

**This medicine contains parabens: methyl p-hydroxybenzoate (E 218), propyl p-hydroxybenzoate (E 216), that may cause allergic reactions (possibly delayed).**

**General:**
- ASPESINE should ne be taken with products containing acetylsalicylic acid (aspirin) or paracetamol.
- As with other acute migraine therapies, before treating a suspected migraine in patients not previously diagnosed as migraineurs, and in migraineurs who present with atypical symptoms, care should be taken to exclude other potentially serious neurological conditions.
- Patients who experience vomitting with > 20 % of their migraine attacks or who require bedrest with > 50 % of their migraine attacks should not use ASPESINE.
- If the patient gets no migraine relief from the first 2-tablet dose of ASPESINE, the patient should seek the advice of a physician.
- prolonged use of any type of painkiller for headaches can make them worse. If this situation is experienced or suspected, medical advice should be obtained and treatment should be discontinued. The diagnosis of medication overuse headache (MOH) should be suspected in patients who have chronic headache (15 days or more per month) with concurrent overuse of headache medications for more than 3 months. Therefore, this product should not be used on more than 10 days per month for more than 3 months.
- Caution should be exercised in patients at risk of being dehydrated (e.g. by sickness, diarrhoea, or before or after major surgery).
- ASPESINE may mask the signs and symptoms of infection due to its pharmadynamic properties.

**Due to the presence of acetylsalicylic acid (aspirin):**

- The concomitant use of acetylsalicylic acid (aspirin) with other systemic NSAIDs, including cyclooxygenase-2 selective inhibitors, should be avoid due to potential for additive undesirable effects (see section 4.5).
- ASPESINE should be used with caution in patients suffering from gout, impaired renal or hepatic function, dehydration, uncontrolled hypertension, and diabetes mellitus.
- Low-dose of acetylsalicylic acid reduces uric acid excretion. For this reason, patients who tend to have reduced uric acid excretion may experience a gout attack.
- Acetylsalicylic acid is known to cause sodium and water retention which can exacerbate hypertension, congestive heart failure, and renal impairment.
- ASPESINE should be used with caution in patients suffering from gout, impaired renal or hepatic function, dehydration, uncontrolled hypertension and diabetes mellitusl.
- ASPESINE should be used with caution in patients suffering from severe glucose-6—phosphate dehydrogenase (G6-PD) deficiency, as acetylsalicylic acid (aspirin) may induce hemolysis or hemolytic anaemia. Factors that may increase the risk of hemolysis are e.g. high dosage, fever or acute infections.
- ASPESINE may lead to an increased bleeding tendency during and after surgical operations (including minor surgeries, e.g. dental extractions) because of the inhibitory effect on platelet aggregation of acetylsalicylic acid (aspirin) which persists for about 4 days after administration.
- Acetylsalicylic acid decreases platelet adhesiveness and increases bleeding time. Hematological and hemorrhagic effects can occur and may be severe. Patients should report any unusual bleeding symptoms to their physician.
- APSESINE should not be taken together with an anticoagulant or other medicinesthat inhibit platelet aggregation without the supervision of a doctor (see section 4.5). Patients with defects of haemostasis should be carefully monitored. Care should be taken in case of metrorrhagia or menorrhagia.
- ASPESINE must be withdrawn immediately if gastrointestinal (GI) bleeding or ulceration occurs in patients receiving this medicinal product. GI bleeding, ulceration or perforation, which can be fatal, have been reported with all NSAIDs and may occur at any time during treatment, with or without warning symptoms or a previous history of serious GI events. They generally have more serious consequences in the elderly. The risk of GI bleeding could be enhanced by alcohol, corticosteroids and NSAIDs (see section 4.5).
- ASPESINE may precipitate bronchospasm and induce asthma exacerbation (so-called intolerance to analgesics/analgesics asthma) or other hypersensitivity reactions. Risk factors are present bronchial asthma, seasonal allergic rhinitis, nasal polyps, chronic obstructive pulmonary disease or chronic infection of the respiratory tract (especially if linked to allergic rhinitis-like symptoms).This applies also to patients showing allergic reactions (e.g. cutaneous reactions, itching, urticaria) to other substances. Special precaution is recommended in such patients (readiness for emergency).
- ASPESINE should not be administered to children and adolescents under 18 years old, unless this is specifically indicated, because there is a possible association between acetylsalicylic acid (aspirin) and Reye's syndrome when administered to children and adolescents. Reye's syndrome is a very rare disease that affects the brain and the liver and that can be fatal.
- Acetylsalicylic acid (aspirin) can interfere with thyroid functional tests due to falsely low concentrations of levothyroxine ($T_4$) or tri-iodothyronine ($T_3$) (see section 4.5).

**Due to the presence of paracetamol:**

- Paracetamol overdose may cause liver failure which may require liver transplant or lead to death. Underlying liver disease increases the risk of paracetamol realted liver damage.
- The overal benefit-risk should be considered in patients diagnosed with liver or kidney impairment before use.
- Cases of hepatic dysfunction/failure have been reported in patients with depleted glutathione levels, particularly in those who are severely malnourished, anorexic, have a low body mass index, or are chronic heavy users of alcohol, or have sepsis.
- In patients with glutathione depleted states, the use of paracetamol may increase the risk of metabolic acidosis.

- The risk of paracetamol toxicity may be increased in patients receiving other potentially hepatotoxic medicinal products or medicinal products that induce liver microsomial enzymes (e.g. rifampicin, isoniazide, chloramphenicol, hypnotics and antiepileptics including phenobarbital, phenytoin and carbamazepine). Patients with history of alcohol abuse are at special risk of hepatic damage (see section 4.5).
- Patients should be warned not to take other products containing paracetamol concurrently due to the risk of severe liver damage in case of overdose (see section 4.9).
- Alcoholic beverages should be avoided while taking this medicine because alcohol use in combination with paracetamol may cause liver damage (see section 4.5).

**Due to the presence of caffein:**
- ASPESINE should be administered with caution to patients with gout, hyperthyroidism and arrhythmia.
- The patient should limit the use of caffeine containing products when taking ASPESINE, as excess caffeine may cause nervousness, irritability, sleeplessness and occasionally rapid heart beat.

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

Drugs combining acetylsalicylic acid, paracetamol and caffeine should not be used together with other non-steroidal anti-inflammatory drugs (NSAIDs) including acetylsalicylic acid and specific cyclooxygenase-2 inhibitors as they may increase the risk of adverse effects.
Medicinal product interactions with other substances that might be caused by each individual ingredient are well-known and there is no indication that those might change through combined use. There are no safety-relevant interactions between acetylsalicylic acid (aspirin) and paracetamol.

**Acetylsalicylic acid (aspirin) (ASA):**

| *Combination with acetylsalicylic acid (aspirin)* | *Possible outcome* |
|---|---|
| Other non-steroidal anti-inflammatory drugs (NSAIDs) | There is an increased risk of GI ulcers and haemorrhages due to synergic effects. If concurrent use is necessary, where appropriate, the use of gastroprotection may be considered for prophylaxis of NSAID-induced GI damage. Thus, concomitant use is not recommended (see section 4.4). |
| Corticosteroids | There is an increased risk of GI ulceration and bleeding, due to synergistic effects. It may be advisable to consider the use of gastroprotection in patients taking ASA and corticosteroids, in particular if they are elderly. Thus, concomitant use is not recommended (see section 4.4). |
| Oral anticoagulants (e.g. coumarine derivatives) | ASA can increase the anticoagulant effect. Clinical and laboratory monitoring of the bleeding time and prothrombin time should be performed. The concomitant use is not recommended (see section 4.4). |
| Thrombolytics | There is an increased risk of bleeding. Particularly, treatment with ASA should not be initiated within the first 24 hours after treatment with alteplase in acute stroke patients. Concomitant use is therefore not recommended (see section 4.4). |
| Heparins & platelet aggregation inhibitors (ticlopidine, clopidogrel, cilostazol) | There is an increased risk of bleeding. Clinical and laboratory monitoring of the bleeding time should be put in place. concomitant use is therefore not recommended (see section 4.4). |
| Selective Serotonin Reuptake Inhibitors (SSRIs) | They could affect coagulation or platelet function when concomitantly taken with ASA, leading to increased occurrence of bleeding in general, and in particular GI bleeding. Therefore, concomitant use should be avoided. |

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| Phenytoin | ASA increases its serum levels; serum phenytoin should be well monitored. |
| Valproate | ASA inhibits its metabolism and hence could increase its toxicity; valproate levels should be well monitored. |
| Aldosterone antagonists (spironolactone, canrenoate) | ASA may reduce their activity due to inhibition of urinary sodium excretion; blood pressure should be well monitored. |
| Loop diuretics (e.g. furosemide) | ASA may reduce their activity due to competition and inhibition of the urinary prostaglandins. NSAIDs can cause acute kidney failure, especially in dehydrate patients. If a diuretic is administered simultaneously with ASA, it is necessary to ensure adequate hydration of the patient and to monitor the kidney function and blood pressure, particularly when starting diuretic treatment. |
| Antihypertensives (ACE-inhibitors, angiotensin II receptor antagonists, calcium-channel blockers) | ASA may reduce their activity due to competition and inhibition of urinary prostaglandins. This combination could lead to acute kidney failure in elderly or dehydrated patients. It is recommended that blood pressure and renal function should be well monitored when starting treatment and the patient should be regularly hydrated. In case of combination with verapamil, the bleeding time should also be monitored. |
| Uricosurics (e.g. probenecid, sulfinpyrazone) | ASA may reduce their activity due to inhibition of tubular resorption, leading to high plasma levels of ASA. |
| Methotrexate ≤ 15 mg/week | ASA, like all NSAIDs, reduces the tubular secretion of methotrexate, increasing its plasma concentrations and thereby also its toxicity. The concomitant use of NSAIDs is therefore not recommended in patients treated with high doses of methotrexate (see section 4.3). The risk of interaction between methotrexate and NSAIDs must also be considered for patients who take low doses of methotrexate, especially those with altered kidney function. If combined treatment is necessary, the complete blood count, liver and kidney functions should be monitored, especially during the first days of treatment. |
| Sulphonylureas and insulin | ASA increases their hypoglycaemic effect, thus some downward readjustment the dosage of the antidiabetic may be appropriate if large doses of salicylates are used. Increased blood glucose controls are recommended. |
| Alcohol | There is an increased risk of GI bleeding; this combination should be avoided. |

**Paracetamol:**

| *Combination with paracetamol* | *Possible complication* |
|---|---|
| Liver enzyme inducers or potentially hepatotoxic substances (e.g. alcohol, rifampicin, isoniazide, hypnotics and antiepileptics including phenobarbital, phenytoin and carbamazepine) | Increased toxicity of paracetamol that could lead to liver damage, even with otherwise harmless doses of paracetamol; therefore, liver function should be monitored (see section 4.4). Concomitant use is not recommended. |
| Chloramphenicol | Paracetamol may increase the risk of elevated plasma concentrations of chloramphenicol. Concomitant use is not recommended. |
| Zidovudine | Paracetamol could increase the tendency to develop neutropenia; therefore, haematological monitoring should be performed. A concomitant use is not recommended, unless monitored by a doctor. |
| Probenecid | It reduces the clearance of paracetamol; thus paracetamol doses should be reduced in case of |

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| | combination with this agent. A concomitant use is not recommended. |
| Oral anticoagulant | The repeated use of paracetamol for more than one week increases anticoagulants effect. Sporadic doses of paracetamol do not have a significant effect. |
| Propantheline or other agents that lead to swoling of gastric emptying | These agents delay paracetamol absorption; a rapid pain relief can be delayed and reduced. |
| Metoclopramide or other agents inducing an acceleration of gastric emptying | These active substances accelerate the absorption of paracetamol, increasing its efficacy and the onset of analgesia. |
| Cholestyramine | It reduces the absorption of paracetamol; therefore cholestyramine should not be given within 1 hour following the administration of paracetamol if a maximal analgesia is targeted. |

**Caffeine:**

| *Combination of caffeine with* | *Possible outcome* |
|---|---|
| Hypnotic agents (e.g. benzodiazepines, barbiturates, antihistaminics, etc.) | The concomitant use can reduce the hypnotic effect or antagonize the anticonvulsive effects of barbiturates. A concomitant use is therefore not recommended. If necessary, the combination can be more useful in the morning. |
| Lithium | Caffeine withdrawal increases serum lithium since renal clearance of lithium can be increased by caffeine, therefore, when caffeine is withdrawn, it may be necessary to reduce the dose of lithium. A concomitant use is then not recommended. |
| Disulfiram | Alcoholic patients who are recovering using treatment with disulfiram must be warned to avoid the use of caffeine in order to avoid the risk of alcohol abstinence syndrome worsening due to caffeine-induced cardiovascular and cerebral excitation. |
| Ephedrine-type substances | Their combination could have an increased dependency potential. A concomitant use is then not recommended. |
| Sympathomimetics or levothyroxine | Their combination might increase the tachycardic effect due to synergistic effects. A concomitant use is then not recommended. |
| Theophylline | A concomitant use might decrease the excretion of theophylline. |
| Quinolone-type antibacterials (ciprofloxacin, enoxacin and pipemidic acid), terbinafine, cimetidine, fluvoxamine and oral contraceptives | Increase of the shelf-life of caffeine due to inhibition of the hepatic cytochrome P-450 pathway; therefore, patients with hepatic disorders, cardiac arrhythmias or latent epilepsy should then avoid caffeine. |
| Nicotine, phenytoin and phenylpropanolamine | They decrease the elimination half-life of caffeine. |
| Clozapine | Caffeine increases serum levels of clozapine due to probable interaction through both pharmacodynamics and pharmacokinetic mechanisms. Serum levels of clozapine should be monitored. A concomitant use is therefore not recommended. |

Interaction with laboratory testing:

- high doses of ASA can affect the results several clinic-chemical laboratory tests.
- Paracetamol intake can affect the results of uric acid when using the phosphotungstic acid method and for glycaemia when using the glucose oxidase/peroxidase method.

- Caffeine can inverse the effects of dipyridamole and adenosine on the myocardial blood flow; thereby interfering with the results of the myocardial imaging tests. It is recommended to suspend the caffeine intake at least 24 hours prior to the test.

## 4.6 Fertility, pregnancy and lactation

Pregnancy
Not recommended during pregnancy. This medicine is contraindicated during the third trimester of pregnancy (see section 4.3).
There are no adequate data available from the use of ASPESINE in pregnant women. Animal studies have not been carried out with acetylsalicylic acid (aspirin), paracetamol and caffeine in combination (see section 5.3).

*Acetylsalicylic acid (Aspirin)*
Due to te presence of acetylsalicylic acid (aspirin) in ASPESINE, its use is contraindicated during the third trimester of pregnancy (see section 4.3) and caution should be exerciced when used in the 2 first terms of pregnancy.

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 prostagladin synthesis inhibitor in early pregnancy. 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 as possible and duration of treatment as short as possible.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may have the following effects:
On the foetus:
- cardiopulmonary toxicity (with premature closure of the *ductus arteriosus* and pulmonaryhypertension);
- renal dysfunction, which may progress to renal failure with oligo-hydroamniosis;

On the mother and new-born:
- At the end of the pregnacy, a possible prolongation of the bleeding time, an anti-aggregating effect that can occur even at very low dose;
- An inhibition of the uterine contractions resulting in a delayed or prolonged labour.

Consequently, acetylsalicylic acid (aspirin) is contraindicated during the third trimester of pregnancy.

*Paracetamol*
A large amount of data on pregnant women demonstrates the absence of any malformations or fetal/neonatal toxicity. Epidemiological studies on the neurodevelopment of children exposed to paracetamol in utero produce inconclusive results. If clinically necessary, paracetamol may be used during pregnancy; however, it should be used at the lowest effective dose, for the shortest possible duration and with the lowest possible frequency.

*Caffeine*
There is evidence that the prolonged intake of high amounts of caffein may lead to spontaneous abortion or premature birth in pregnant women. Non-clinical studies have shown reproductive toxicity at very high doses.

Breast-feeding

Salicylate, paracetamol and caffeine are excreted into breast milk.
Due to the content of caffeine, the behaviour of the suckling child may be influenced (excitement, poor sleeping pattern). Because of the salicylate, there may also be a potential for adverse effects on the platelet function in the infant (could cause slight bleeding), even if none have been reported. There are also some concerns regarding the use of ASA in case of potential development of Reye's syndrome in infants. Therefore, APSESINE is then not recommended during breast-feeding.

Fertility
*Acetylsalicylic acid (Aspirin)*
There is some evidence that medicines inhibiting cyclo-oxigenase/prostaglandins synthesis may cause impairment of female fertility because of an effect on ovulation. This effect is reversible after withdrawal of the treatment.

## 4.7 Effects on ability to drive and use machines

The effects on the ability to drive vehicules or use machines have not been studied. If you notice undesirable effects as dizziness or drowsiness, you should not drive or use machines. Talk to your doctor as soon as possible.

## 4.8 Undesirable effects

Many of the following adverse reactions are clearly dose-dependent and variable from one person to another.

The below table provides a listing of adverse reactions from 16 single-dose clinical studies on the efficacy and safety of the association acetylsalicylic acid (aspirin)/paracetamol/caffeine in the treatment of migraine, headache or dental pain associated with tooth extraction, involving 4809 subjects treated with the association, and from post-marketing spontaneous reports.

The adverse reactions included in the table were those regarded as at least possibly related to the administration of the association acetylsalicylic acid (aspirin)/paracetamol/caffeine and are listed in descending order of frequency within MedDRA System Organ Classification.

For the undesirable effects reported in the frame of the spontaneous declaration system, the frequencies cannot be determined reliably and are, thus, unknown.

The undesirable effects are ranked by organ class system and by frequency. The frequencies are defined as follows: very common (≥ 1/10), common ≥ 1/100, < 1/10), uncommon (≥ 1/1,000, < 1/100), rare (≥ 1/10,000, < 1/1.000), very rare (< 1/10,000), including isolated reports and unknown frequency (cannot be estimated based on the available data).

Table of adverse reactions reported from clinical studies and from post-marketing spontaneous reports:

| Organ class system | Frequency | Preferred term |
|---|---|---|
| Infections and infestations | Rare | Pharyngitis |
| Blood and lymphatic system disorders | Not known | Prolonged bleeding time, thrombocytopenia, ecchymosis |
| Immune system disorders | Undetermined frequency | Hypersensitivity*, anaphylactic reaction, |
| Metabolism and nutrition disorders | Rare | decrease appetite |
| | Undetermined frequency | Sodium and water retention |
| Psychiatric disorders | Common | Nervousness |
| | Uncommon | Insomnia |
| | Rare | Anxiety, euphoric mood, tension |

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|---|---|---|
| | Undetermined frequency | Agitation |
| Nervous system disorders | Common | dizziness |
| | Uncommon | Tremor, paraesthesia, headache |
| | Rare | Dysgeusia, attention disorder, amnesia, abnormal coordination, hyperaesthesia, sinus headache |
| | Undetermined frequency | Migraine, somnolence |
| Eye disorders | Rare | Eye pain, visual disturbance |
| Ear and labyrinth disorders | Uncommon | Tinnitus |
| | Undetermined frequency | Temporary loss of hearing |
| Cardiac disorders | Uncommon | Arrhythmia |
| | Undetermined frequency | Palpitation |
| Vascular disorders | Rare | flushing, peripheral vascular disorder |
| | Undetermined frequency | Hypotension |
| Respiratory, thoracic and mediastinal disorders | Rare | Epistaxis, hypoventilation, rhinorrhoea |
| | Undetermined frequency | Dyspnoea, asthma, bronchospasm |
| Gastro-intestinal disorders | Common | Nausea, abdominal discomfort |
| | Uncommon | Dry mouth, diarrhoea, vomiting |
| | Rare | Eructation, flatulence, dysphagia, oral paraesthesia; salivary hypersecretion |
| | Undetermined frequency | Upper abdominal pain, dyspepsia, abdominal pain, GI haemorrhage (including upper GI haemorrhage, gastric haemorrhage, gastric ulcer haemorrhage, duodenal ulcer haemorrhage, rectal haemorrhage), GI ulcer (including gastric ulcer, duodenal ulcer, large intestinal ulcer, peptic ulcer), gastritis |
| Hepatobiliary disorders | Undetermined frequency | Liver failure, increased levels of liver enzymes, Reye's syndrome (section 4.3) |
| Skin and subcutaneous tissue disorders | Rare | Hyperhidrosis, pruritus, urticaria |
| | Undetermined frequency | Erythema, skin rash, angioedema, erythema multiform |
| Musculoskeletal and connective tissue disorders | Rare | Musculoskeletal stiffness, neck pain, back pain, muscular spams |
| Kidney and urinary disorders | Undetermined frequency | Kidney dysfunction, increased blood levels of uric acid |
| General disorders and administrations site conditions | Uncommon | Fatigue, felling jittery |
| | Rare | Asthenia, chest discomfort |
| | Undetermined frequency | Malaise, feeling abnormal |
| Investigation | Uncommon | Increased heart rate |

*including rhinitis
Very cases of severe skin reactions have been reported.

There is no information available to suggest that the extent and type of adverse events of the individual substances is enhanced or the spectrum broadened when the fixed combination is used as instructed.
The increased risk of bleeding can persist for 4 to 8 days after taking acetylsalicylic acid (aspirin). Severe bleeding is very rarely observed (e.g. intracerebral bleeding), in particular in patients with untreated hypertension and/or who have a concomitant anticoagulant treatment. These bleedings can, in isolated cases, be life threatening.

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

**Related to acetylsalicylic acid (aspirin):**
The symptoms of a mild intoxication with acetylsalicylic acid (aspirin) include dizziness, tinnitus, deafness, sweating, warm extremities with bounding pulses, nausea and vomiting, dehydration, headache and confusion. These symptoms can occur at plasma levels of 150 to 300 µg/ml. they can be controlled by decreasing the dose or interrupting the treatment.
A more serious intoxication occurs at concentrations above 300 µg/ml. Symptoms of severe overdose include hyperventilation, fever, restlessness, ketosis, respiratory alkalosis and metabolic acidosis. A CNS depression can lead to a coma. A cardiovascular collapse and respiratory failure can also occur.

Uncommon symptoms include haematemesis, hyperpyrexia, hypoglycaemia, hypokalaemia, thrombocytopenia, increased INR/PTR, intravascular coagulation, renal failure and non-cardiac pulmonary oedema. Central neurological symptoms such as confusion, disorientation, coma and convulsions are less common in adults than in children.

Treatment of a severe overdose:
The patient should be transferred to hospital and the poison control center contacted immediately. When it is suspected that the patient has taken more than 120 mg/kg of salicylates within the last hour, Administration of repeated doses of activated charcoal oral can be administered.

The plasma concentration should be measured in patients having ingested more than 120 mg/kg of salicylates, although the severity of the poisoning cannot be determined from these alone. The clinical and biochemical characteristics should also be taken into account.

In plasma concentrations exceeding 500 micrograms/ml (350 micrograms/ml in children under 5 years of age) the intravenous administration of sodium bicarbonate is effective in removing salicylate from the plasma. Forced diuresis should not be used alone since it does not enhance salicylate excretion and may cause pulmonary oedema.
Hemodialysis or hemoperfusion are the methods of choice in cases where the plasma salicylate concentration is greater than 700 micrograms / ml, or lower in children and the elderly people, or
if there is a severe metabolic acidosis.

**Related to paracetamol**
An overdose (> 10 g in total in adult or > 150 mg/kg in a single intake) can cause hepatic cytolysis that can result in a complete and irreversible necrosis (hepatic failure, metabolic acidosis, renal failure) and, eventually a coma and potentially death, or pay required a liver transplant. Less commonly, a renal tubular necrosis may develop.

Early signs of overdose (very commonly nauseas, vomiting, anorexia, pallor, lethargy and sweating) appear within the first 24 hours.

Abdominal pain can be the first sign of liver failure, which is usually not visible during the first 24 or 48 hours, and that can appear only 4 to 6 hours following the ingestion. Hepatic damage is generally observed after a maximum of 72 to 96 hours after the ingestion. Glucose metabolism anomalies and metabolic acidosis can occur. Acute renal failure – with acute tubular necrosis – can develop even in the absence of severe hepatic damage. Cases of cardiac arrhythmia and of pancreatitis have been reported.

Patients are considered at high risk when receiving enzyme-inducing medicinal products, such as carbamazepine, phenytoin, phenobarbital, rifampicin and St John's wort, or when they have history of excessive alcohol consumption or suffer from malnutrition.

Treatment of an overdose:
Urgent medical treatment is necessary in case of overdose, even if symptoms of overdose are not present.
If overdosage is suspected or confirmed, seek the advice of the Poison Control Centre immediately and refer the patient to the nearest Emergency Department for treatment management and expertise. This should also happen in patients without symptoms or signs of overdose due to the risk of delayed liver damage.
When it is suspected that the patient has ingested more than 150 mg/kg of paracetamol within the last hour, repeated doses of activated charcoal should be administered orally. However, if acetylcysteine or methionine is to be given by mouth, it is preferable to remove the charcoal from the stomach to prevent it from reducing the absorption of the antidote.

Antidotes:
N-acetylcysteine should be administered intravenously or orally as soon as possible after ingestion. It is the most effective within the first 8 hours following the overdose. The effect of the antidote decreases progressively then. Nevertheless, it has been demonstrated that a treatment during 24 hours and more after the ingestion remains beneficial.

Methionine is most effective within the first 10 hours after ingestion of paracetamol overdose. following the overdose of paracetamol. Hepatic damage is more frequent et more severe if the treatment with methionine is initiated more than 10 hours after ingestion.

Oral absorption might be reduced by vomiting or activated charcoal.

**Related to caffeine**
The usual symptoms include epigastric pain, vomiting, anxiety, nervousness, restlessness, insomnia, excitement, muscular twitching, confusion, tremors and convulsions. In case of significant caffeine intake, hyperglycaemia can also appear. Heart symptoms include tachycardia and cardiac arrhythmia. Symptoms are controlled by reducing or stopping caffeine intake.
Clinically significant symptoms of caffeine overdose occur with this association if the amount ingested is associated with a serious paracetamol-related liver toxicity.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other analgesics and antypiretics; acetylsalicylic acid (aspirin) and derivatives, ATC code: N02BA51

Mechanism of action
Acetylsalicylic acid (Aspirin) has analgesic, antipyretic and anti-inflammatory properties, mainly due to the inhibition of the biosynthesis of prostaglandins and thromboxanes from arachidonic acid, by the irreversible acetylation of the cyclooxygenase enzyme (COX).

Paracetamol has analgesic and antipyretic properties, but unlike acetylsalicylic acid (aspirin), it does not inhibit platelet aggregation.

The addition of caffeine increases the antinociceptive effects of acetylsalicylic acid (aspirin) and paracetamol.

Pharmacodynamic effects
*Acetylsalicylic acid*

Acetylsalicylic acid is an anti-inflammatory, mainly by inhibiting inflammatory mediators via inhibition of cyclooxygenase in peripheral tissues. This suppression of the cyclooxygenase pathway in peripheral tissues may lead to its first adverse effect of gastric irritation.
Low doses of acetylsalicylic acid affect platelet aggregation by irreversible inhibition of platelet cyclooxygenase (COX-1). This effect lasts for the life of the platelet and prevents the formation of thromboxane coagulation factor A2. At higher doses (above 150-300 mg/day) acetylsalicylic acid reversibly inhibits the formation of cyclooxygenase-dependent prostaglandin I2 (prostacyclin) in endothelial cells. Prostaglandin I2 is an arterial vasodilator and inhibits platelet aggregation, however there is no evidence that aspirin is thrombogenic in humans.

*Paracetamol*
Central mechanisms of action have been proposed for paracetamol and peripheral tissues can be influenced differently. For the protective prostaglandins of the gastrointestinal tract, only a slight inhibitory effect of paracetamol has been reported.

*Caffeine*
Caffeine increases the analgesic effect of paracetamol and acetylsalicylic acid and shortens the time to onset of analgesic effect.

Migraine studies
The efficacy of the association acetylsalicylic acid (aspirin)/paracetamol/caffeine in the treatment of acute migraine attacks was confirmed in 3 single-dose, double-blinded, placebo-controlled studies and in 2 single-dose, double-blind, placebo and active controlled studies, one versus ibuprofen 400 mg and the other one versus sumatriptan 50 mg. In these studies, single dose of the association acetylsalicylic acid (aspirin)/paracetamol/caffeine consisted of in 500 mg of aspirin, 500 mg of paracetamol, and 130 mg of caffeine.

In the three placebo-controlled studies, the association acetylsalicylic acid (aspirin)/paracetamol/caffeine was superior to placebo in reducing migraine pain intensity to mild or none 2 hours after dose in the drug–treated patients. It started relieving migraine symptoms, such as migraine pain, within 30 minutes.

In a placebo and active controlled study, the association and ibuprofen (2 tablets of ibuprofen 200 mg) were compared in the treatment of migraine. The association was shown to deliver significantly greater pain relief than ibuprofen starting at 2 hours post dose and to deliver clinically meaningful pain relief 20 minutes faster.
In another placebo and active controlled pilot study, the combination was compared with sumatriptan 50 mg and placebo for the early treatment of migraine. In this study the association was shown to be significantly more effective than sumatriptan 50 mg at reducing migraine pain intensity throughout the 4-hour treatment period. Sumatriptan 50 mg was shown to be superior to placebo with respect to this variable, but not to a statistically significant degree.

In a separate placebo and active controlled post-marketing study, the combination was not shown to be non-inferior to sumatriptan 100 mg. However, in the acute treatment of migraine, the association provided pain and symptom relief over 24 hours

Overall, the efficacy of the association acetylsalicylic acid (aspirin)/paracetamol/caffeine has been demonstrated for the relief of migraine symptoms such as headaches, nausea, sensitivity to light and noise and functional incapacity.

Headachestudies
The efficacy of the association acetylsalicylic acid (aspirin)/paracetamol/caffeine was assessed in 4 independent multi-center, double-blinded,
paracetamol 1000 mg and placebo-controlled crossover studies in the treatment of episodic tension-type headache. In all these studies, the combination showed systematically to be superior to placebo and active controls (mono-substances) regarding all the measures of efficacy, intensity and pain relief over all the observation period.

Another multi-centre, double-blinded clinical study conducted in tension headaches, compared the onset of analgesia between the association, placebo, and ibuprofen 400 mg. In this study, the subjects treated with the combination of acetylsalicylic acid (aspirin)/paracetamol/caffeine showed a significantly increased pain relief than subjects treated with the placebo, between 15 minutes and 4 hours. This observation was clear for both assessment criteria Pain relief and Responders.

## 5.2 Pharmacokinetic properties

**Acetylsalicylic acid (Aspirin)**

Absorption

After oral administration, acetylsalicylic acid is completely resorbed in the gastrointestinal tract. Approximately 70% of a dose of acetylsalicylic acid reaches the circulation unchanged; the remaining 30% is hydrolysed to salicylic acid during absorption by esterases in the gastrointestinal tract, liver or plasma. The plasma concentration peak of salicylate is reached in 1 to 2 hours with single doses. Food reduces the speed but not the extent of absorption.

Distribution

Salicylic acid is widely distributed in all body tissues and fluids, including the central nervous system. The highest concentrations are found in plasma, liver, renal cortex, heart and lungs. Acetylsalicylic acid and salicylic acid bind partially to serum proteins, mainly albumin. The protein binding of salicylate is concentration-dependent, i.e. non-linear. At low concentrations (< 100 micrograms/millilitre (mcg/mL)), about 90% of the plasma salicylate is bound to albumin, while at higher concentrations (> 400 (mcg/mL)) only 40-70% is bound. Salicylic acid crosses the placenta and is excreted in breast milk.

Metabolism

Acetylsalicylic acid is hydrolysed in plasma to salicylic acid (with a half-life of 15-20 minutes) so that plasma levels of acetylsalicylic acid are essentially undetectable 1-2 hours after administration. Salicylic acid is mainly conjugated in the liver to form salicyluric acid by conjugation with glycine, salicyl phenolic glucuronide and salicyl acyl glucuronide by conjugation with glucuronic acid, and a number of minor metabolites. After a single dose of 1 g of acetylsalicylic acid, the average half-life of salicylic acid is about 6 hours. Salicylate metabolism is saturable, and total body clearance decreases at higher serum concentrations because of the limited ability of the liver to form both salicyluric acid and phenolic glucuronide. The half-life of salicylate varies with dosage. Following toxic doses (10-20 grams (g)), the plasma half-life may be increased to more than 20 hours.

Elimination

Salicylic acid and its metabolites are excreted by the kidneys. Renal excretion of unchanged drug depends on the urinary pH. When the urinary pH rises from 5 to 8, a greater fraction of the administered dose is eliminated as free salicylic acid, and renal clearance of free salicylic acid increases from <5% to >80%. At therapeutic doses, approximately 10% is excreted in the urine as salicylic acid, 75% as salicyluric acid, and 10% phenolic and 5% acyl glucuronides of salicylic acid.

**Paracetamol**

Absorption

Paracetamol is rapidly absorbed from the gastrointestinal tract, with peak plasma concentration occurring approximately 30 minutes to 2 hours after ingestion.

Distribution

Plasma protein binding is negligible at usual therapeutic concentrations but increases with increasing concentrations.

Metabolism

Paracetamol is metabolised in the liver and excreted in the urine, mainly in the form of glucurono and sulpho-conjugates. A minor hydroxylated metabolite which is usually produced in very small amounts

in the liver by mixed-function oxidases, and which is usually detoxified by conjugation with hepatic glutathione, may accumulate after an overdose of paracetamol and cause liver damage.

Elimination
Less than 5% is excreted as unchanged paracetamol. The elimination half-life varies from about 1 to 4 hours.

**Caffeine**

Absorption
Caffeine is completely and rapidly absorbed after oral administration, with peak concentrations occurring between 5 and 90 minutes after intake in fasted subjects. There are no signs of pre-systemic metabolism.

Distribution
Caffeine is distributed in all body fluids. The binding average of caffeine to plasma proteins is 35%.

Metabolism
Caffeine is almost completely metabolised by oxidation, demethylation and acetylation and is excreted in the urine. The main metabolites are 1-methylxanthine, 7-methylxanthine and 1,7-dimethylxanthine (paraxanthine). Minor metabolites include 1-methyluric acid and 5-acetylamino-6-formylamino-3-methyluracil (AMFU).

Elimination
Elimination is almost entirely by hepatic metabolism in adults. In adults, there is a high individual variability in the rate of elimination. The mean plasma elimination half-life is 4.9 hours, with a range of 1.9-12.2 hours.

**Combination**
In the combination of the three active ingredients, the quantity of each substance is low. Then, there is no saturation in the elimination process with the potential risks related to an increase in half-life and toxicity.

The pharmacokinetic data of the fixed-dose combination of acetylsalicylic acid (aspirin), paracetamol and caffeine are conforming to the pharmacokinetic profile established for each individual substance or for the combination of each analgesic with caffeine.

There are neither any known critical drug-drug interactions between acetylsalicylic acid (aspirin), paracetamol and caffeine, nor any increase in the risk of interaction with other medicinal products through their combined use are known. Findings with respect to pharmacokinetics of the association acetylsalicylic acid (aspirin)/paracetamol/caffeine were as expected and no interaction between the 3 active substances were observed.

## 5.3 Preclinical safety data

**Acetylsalicylic acid (Aspirin)**

Preclinical studies carried out on animals using acetylsalicylic acid (aspirin) do not show ony organ toxicity, except the effects on gastrointestinal mucosae and, a high doses, kidney damage. Acetylsalicyl acid is neither mutagenic, nor carcinogenic.
It was observed that salicylates have teratogenic effects a toxic doses for the mother in a certain number of animal species (for instance, cardiac and skeletal malformation, abnormality of the middle line) there were reports on an implantation disorder, embryotoxic and foetotoxic effects and a learning ability disorder in the offspring following prenatal exposition.

**Paracetamol**

The prenical data from the conventional pharmacological studies of safety, repeated-dose toxicology, geotoxocity, carcinogenesis or reproductive toxicity have not showed any particular risk for humans at relevant therapeutic doses. Conventional studies using currently accepted standards for the evaluation of the toxicity to reproduction and development are not available. An overdose can result in serious hepatotoxicity.

**Caffeine**
Caffein was shown to be devoid of mutagenic and oncogenic risk. In animal studies in different species (rat, mice, rabbit), very high doses of caffein were associated with an increase in birth defects.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Sodium starch glycolate, maize starch, microcrystalline cellulose, gelatin, methyl parahydroxybenzoate (E 218), propyl parahydroxybenzoate (E 216), erythrosine supra (E 127), purified talc, colloidal silicon dioxide, stearic acid.

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

3 years

### 6.4 Special precautions for storage

Do not store above 30 °C.

### 6.5 Nature and contents of container

Pouch of 4 tablets in low density polyethylene laminated paper packaging, box groupping of 20 or 100.

### 6.6 Special precautions for disposal

No special requirements.

## 7. CATEGORY OF DISTRIBUTION

☒ OTC (over-the counter medicine) ☐ POM (Prescription only medicines)

## 8. MARKETING AUTHORISATION HOLDER

Exphar s.a.
Zoning Industriel de Nivelles Sud, Zone 2
Avenue Thomas Edison 105
1402 Thines (Belgium)

## 9. MANUFACTURER

Milan Laboratories (India) Pvt. Ltd.

Plot no 63-67 & 87, Jawahar co.op. Industrial Estate, ltd
Kamothe, Panvel, Distric Thane
Maharashtra - 410209
INDIA

## 10. DATE OF REVISION OF THE TEXT

07/2022