SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT AND INTERNATIONAL NONPROPRIETARY NAME (INN)

TOPIRIN tablets (250+250+50) mg

acetylsalicylic acid +paracetamol+ caffeine

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains contains 250 mg of Acetylsalicylic acid, 250 mg of Paracetamol and 50 mg of Caffeine.

3. PHARMACEUTICAL FORM

Tablets.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

For the treatment of mild to moderate pain including headache, migraine, neuralgia, toothache, sore throat, period pains, symptomatic relief of sprains, strains, rheumatic pain, sciatica, lumbago, fibrositis, muscular aches and pains, joint swelling and stiffness, influenza, feverishness and feverish colds.

4.2. Posology and method of administration

Unless otherwise is prescribed, adults and children older than 16 years should take 1 to 2 TOPIRIN tablets (equivalent to 250-500 mg of aspirin, 250-500 mg of paracetamol and 50-100 mg of caffeine), if necessary, up to three times a day (usually in the interval of 4 to 8 hours).
The maximum daily dose for adults and children over 16 years is TOPIRIN two tablets three times a day (equivalent to 1,500 mg of aspirin, paracetamol 1500 mg and 300 mg of caffeine).
To prevent the risk of overdose, it should ensure that other medications that are applied at the same time, do not contain paracetamol.
Tablets are taken dissolved in a liquid, or swallowed whole with plenty of liquid. The drug can not be used without medical or dental advice for more than three to four days and are not for us in higher doses.

4.3. Contraindications

TOPIRIN tablets should not be used:

• in case of hypersensitivity to aspirin, salicylates or other NSAIDs, paracetamol, or any of the other substances in the tablets TOPIRIN
• in gastric and intestinal bleeding
• with severe liver damage
• with severe renal impairment
• with severe, uncontrolled heart failure
• with hemorrhagic diathesis
• concomitant treatment with methotrexate 15 mg per week or more
• in the last three months of pregnancy
• For children younger than 16 years.

The drug should be used only after consulting your doctor:
• with concomitant therapy with oral anticoagulants, systemic acting heparin, thrombolytics and platelet

inhibitors
• for bronchial asthma, allergic rhinitis and nasal polyposis
• in case of hypersensitivity to allergens
• chronic and recurring problems with the stomach or intestines
• For existing kidney damage or kidney problems
• with liver damage
• in the lack of glucose-6-phosphate dehydrogenase
• with Gilbert syndrome
• prior to surgery
• gastrointestinal symptoms, gastrointestinal ulcers in history, gastrointestinal bleeding or perforation
• with hyperthyroidism.

4.4. Special warnings and precautions for use

Caution should be exercised in patients with asthma, allergic disease, impairment of hepatic or renal function (avoid if severe) and dehydration. The hazards of overdose are greater in those with non-cirrhotic alcoholic liver disease.
Do not take if you have a stomach ulcer.
Do not take more medicine than the label tells you to. If you do not get better, talk to your doctor.
Do not take anything else containing paracetamol while taking this medicine.
Talk to your doctor at once if you take too much of this medicine, even if you feel well. This is because too much paracetamol can cause delayed, serious liver damage.
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 under 16 years unless specifically indicated (e.g. Kawasaki's disease).
Patients should be advised that paracetamol may cause severe skin reactions. If a skin reaction such as skin reddening, blisters, or rash occurs, they should stop use and seek medical assistance right away.

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

Acetylsalicylic acid may increase the effects and side effects of the following medicines:
• anticoagulants, antiplatelet agents (eg. Ticlopidine), thrombolytics, SSRI: increased risk of bleeding
• NSAIDs, corticosteroids, or concomitant use of alcohol: increased risk of gastrointestinal symptoms (eg. Gastrointestinal bleeding)
• antidiabetic drugs, valproic acid, methotrexate, digoxin, lithium.

Acetylsalicylic acid can reduce the effects of the following medicines
• diuretics (eg., Aldosterone)
• uricosuric agents (eg., Probenecid, sulfinpyrazone, benzbromarone)
• antihypertensives.
When concomitant administration of inducers of liver enzymes such as barbiturates, antiepileptics, and rifampicin, otherwise harmless doses of paracetamol can cause liver damage, the same as with alcohol abuse.
Simultaneous use of resources, which lead to the slowing of gastric emptying, such as propantheline, can delay the absorption and onset of action of paracetamol.
Co-administration procinetickas like metoclopramide, may increase the absorption and accelerate the onset of action of paracetamol.
Concomitant use of paracetamol and chloramphenicol inhibits elimination of chloramphenicol, which increases the risk of side effects.
Co-administration of paracetamol and zidovudine enhances the tendency of neutropenia. This drug should therefore be used with zidovudine only under medical supervision.

Other known effects
• probenecid, salicylamide: decreased elimination of paracetamol, an increased risk of side effects
• oral anticoagulants: increased risk of bleeding with concomitant administration of paracetamol 7 or more days.

• cholestyramine: reduced absorption of paracetamol
Taking paracetamol may affect the determination of uric acid by the sodium salt and glucose in blood using glucose oxidase-peroxidase.
Caffeine antagonize the sedative effect of many drugs, such as barbiturates, antihistamines, etc..
Caffeine works synergistically to effects such as tachycardia. sympathomimetic, thyroxine, etc.
For drugs with a wide spectrum of action, the interaction can not be easily distinguished in detail, nor to predict (eg. Benzodiazepines).
Oral contraceptives, cimetidine, disulfiram can reduce the degradation of caffeine in the liver.
Barbiturates and smoking is accelerating.
The excretion of theophylline decreased the influence of caffeine. Caffeine increases the potential dependence on efedrin.Concomitant use with gyrase inhibitors, type quinoline carboxylic acid can delay the elimination of caffeine and its degradacijskog products Paraxanthine.
There is no evidence that it is possible potential addiction to analgesics, such as acetylsalicylic acid or acetaminophen, increased due to caffeine. Based on theoretical considerations and existing knowledge, potential misuse of caffeine in combination with aspirin or acetaminophen, is not represented.
Long-term use of the fixed combination, while exposure to nephrotoxic substances and existing kidney damage, genetic predisposition syndrome or propensity for kidney damage, may lead to increased risk of analgesic nephropathy.

4.6. Pregnancy and lactation

There is clinical and epidemiological evidence of safety of aspirin in pregnancy, but it may prolong labour and contribute to maternal and neonatal bleeding, and so should not be used in late pregnancy.

Aspirin appears in breast milk, and regular high doses may affect neonatal clotting. Not recommended while breast-feeding due to possible risk of Reye's Syndrome as well as neonatal bleeding due to hypoprothrombinaemia.

Epidemiological studies in human pregnancy have shown no ill effects due to paracetamol used in the recommended dosage, but patients should follow the advice of the doctor regarding its use.
Paracetamol is excreted in breast milk but not in a significant amount. Available published data do not contraindicate breast feeding.

Caffeine appears in breast milk. Irritability and poor sleeping pattern in the infant have been reported.

4.7. Effects on ability to drive and use machines

None stated.

4.8. Undersirable effects

Adverse reactions are ranked by frequency, the most frequent first, using the following convention:
• 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), including isolated reports
Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.

In the placebo-controlled trials in 1143 patients receiving the fixed combination of ASA, acetaminophen and caffeine, the following side effects have been reported:

Psychic:
Common: Nervousness
Rare: Agitation

Nervous system:
Common: Dizziness
Rare: Agitation
Ears:
Rare: Vertigo
Heart:
Occasional: Palpitations
Rare: Tachycardia
Gastrointestinal tract:
Common: Abdominal pain, dyspepsia, nausea
Occasional: Vomiting
Rare: diarrhea, esophagitis
Skin:
Rare: Hyperhidrosis
General information:
Rare: Exhaustion

Other side effects, or more frequently than indicated or individual adverse drug reactions TOPIRIN tablets will be listed below.
Aspirin
List of the undesirable effects that include all known side effects during treatment with aspirin, even in long-term treatment of rheumatic patients at high doses. When using the higher dose, the more likely are gastrointestinal upset.
Blood and lymphatic system
The frequency is not known: Bleeding such as nosebleeds, bleeding gums, or bleeding of the skin with possible prolongation of bleeding time. This effect can last for more than 4-8 days after the cessation of drug consumption.
The immune system
Occasional: Hypersensitivity reactions (skin reactions)
Rare: hypersensitivity reactions such as dyspnoea, hypotension, anaphylaxis, angioedema, serious skin reactions (including erythema multiforme),
Endocrine System
Very rare: hypoglycaemia
Nervous system
The frequency is not known: Headache, drowsiness and mental confusion may be signs of an overdose.
Eyes
The frequency is not known: Blurred vision
Ears
The frequency is not known: a disorder of hearing, ringing in the ears
Gastrointestinal tract
Common: abdominal pain, gastrointestinal symptoms such as stomach pain, micro bleeding, heartburn, nausea and vomiting
Rare: gastrointestinal ulcers and bleeding, which can rarely lead to anemia.
Very rare: gastrointestinal perforation
Occasional: diarrhea
The frequency is not known: erosive gastritis
Liver
Very rare: elevated levels of transaminases, liver dysfunction
Kidney
Very rare: renal dysfunction

Paracetamol:
Blood and lymphatic system
Very rare: blood disorders including thrombocytopenia, leukopenia, pancytopenia, agranulocytosis
The immune system
Very rare: hypersensitivity reactions, including erythema, urticaria, dizziness, angioneurotic edema, sweating, dyspnea, hypotension and anaphylactic shock, bronchospasm in patients who are allergic to NSAIDs
Liver

Rare: increased transaminases
Skin
Rare: Redness
In some cases, it is described that the deterioration of the inflammation caused by the infection time associated with systemic administration of NSAIDs (such as development nekrozirajućeg fasciitis). This is probably associated with the anti-inflammatory mechanism of action of NSAIDs.

If during the use of the drug TOPIRIN tablets new signs of infection occur or worsen existing, the patient is advised to immediately seek medical help. Consideration should be given to whether there is an indication for anti-infectious / antibiotic therapy.
No findings using a fixed combination may be determined by increasing the scope and nature of certain side effects or expansion of their spectrum.
The content of caffeine in TOPIRIN tablets can cause insomnia, restlessness, tremors, rapid pulse and stomach problems.

4.9. Overdose

This product contains both paracetamol and aspirin, and as such, any overdose events should be assessed using information available on both active substances.

Liver damage is possible in adults who have taken 10g or more of paracetamol. Adults who have consumed more than 5g of paracetamol, may experience liver damage if they have one of the following risk factors:

• long term treatment with either anti-infectives, anti-epileptics or St John's Wort, or any other drugs that induce liver enzymes

• regular consumption of ethanol in excess of recommended amounts

• likely to be glutathione deplete e.g. eating disorder, cystic fibrosis, HIV infection, starvation, cachexia.

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.

Symptoms

Common features exist for both active substances when taken in overdose, but these can be tabulated as follows:

Paracetamol	Acetylsalicylic acid	Caffeine

Within the first 24 hours: Pallor Nausea Vomiting Anorexia Abdominal pain After 12-48 hours: Liver damage Abnormalities of glucose metabolism and metabolic acidosis Severe poisoning: Hepatic failure may progress to encephalopathy, haemorrhage, hypoglycaemia, cerebral oedema and death. With or without severe liver damage: Acute renal failure with acute tubular necrosis strongly suggested by loin pain haematuria and proteinuria. Cardiac arrhythmias Pancreatitis	Common: Vomiting, Dehydration, Tinnitus Vertigo, Deafness, Sweating Warm extremities with bounding pulses Increased respiratory rate Hyperventilation Acid base disturbance Mixed respiratory alkalosis and metabolic acidosis with normal or high arterial pH (normal or reduced hydrogen ion concentration) in adults and children aged over 4 years. In children aged 4 years or less, a dominant metabolic acidosis with low arterial pH (raised hydrogen ion concentration) is common. Acidosis can increase salicylate transfer across the blood brain barrier. Uncommon: Haematemesis Hyperpyrexia Hypoglycaemia Hypokalaemia Thrombocytopenia Increased INR/PTR Intravascular coagulation Renal failure Non-cardiac pulmonary oedema Confusion, disorientation, coma and convulsions are more common in children than adults.	Other symptoms of overdosage, associated with the caffeine component, include: CNS stimulation; anxiety, nervousness, restlessness, insomnia, excitement, muscle twitching, confusion, convulsions Cardiac: tachycardia, cardiac arrhythmia Gastric: Abdominal or stomach pains Other: diuresis, facial flushing

Management

Paracetamol:

Immediate treatment is essential in the management of overdose due to the paracetamol content of the product.

There may be few or no initial symptoms, and these can be limited to nausea or vomiting and may not reflect the severity of overdose or the risk of organ damage. Management should be in accordance with established treatment guidelines, see BNF overdose section.

Treatment with activated charcoal should be considered if the overdose has been taken within 1 hour.

Plasma paracetamol concentrations should be measured at 4 hours or later after ingestion (earlier concentrations are unreliable).

Treatment with N-acetylcysteine may be used up to 24 hours after ingestion of paracetamol; however, the maximum protective effect is obtained up to 8 hours post-ingestion. The effectiveness of the antidote declines sharply after this time. If required the patient should be given intravenous N-acetylcysteine, in line with the established dosage schedule. If vomiting is not a problem, oral methionine may be a suitable alternative for remote areas, outside hospital.

Management of patients who present with serious hepatic dysfunction, or are under 10 years or over 70, beyond 24h from ingestion should be discussed with the National Poisons Information Service (NPIS) or a liver unit.

Salicylates:

Treatment with activated charcoal should be considered if salicylate plasma concentration is greater than 250mg/kg.

Plasma salicylate concentrations should be measured although the severity of poisoning cannot be determined from this alone and the clinical and biochemical features must be taken into account.

Elimination of aspirin is increased by urinary alkalinisation, which is achieved by the administration of 1.26% sodium bicarbonate. The urine pH should be monitored. Metabolic acidosis should be corrected with intravenous 8.4% sodium bicarbonate (first check serum potassium). Forced diuresis should not be used since it does not enhance salicylate excretion and may cause pulmonary oedema.

Haemodialysis is the treatment of choice for severe poisoning and should be considered in patients with plasma salicylate concentrations >700 mg/L (5.1 mmol/L), or lower concentrations associated with severe clinical or metabolic features.

Patients under 10 years or over 70 years of age may be at an increased risk of salicylate toxicity and may require dialysis at an earlier stage.

Caffeine:

Treatment of caffeine overdose is primarily symptomatic and supportive. Diuresis should be treated by maintaining fluid and electrolyte balance and CNS symptoms can be controlled by intravenous administration of diazepam.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Acetylsalicylic acid

Mechanisms of action/effect

Salicylates inhibit the activity of the enzyme cyco-oxygenase to decrease the formation of precursors of prostaglandins and thromboxanes from arachidonic acid. Although many of the therapeutic effects may result from inhibition of prostaglandin synthesis (and consequent reduction of prostaglandin activity) in various tissues, other actions may also contribute significantly to the therapeutic effects.

Analgesic

Produces analgesia through a peripheral action by blocking pain impulse generation and via a central action, possibly in the hypothalamus.

Anti-inflammatory (Non-steroidal)

Exact mechanisms have not been determined. Salicylates may act peripherally in inflamed tissue probably by inhibiting the synthesis of prostaglandins and possibly by inhibiting the synthesis and/or actions of other mediators of the inflammatory response.

Antipyretic

May produce antipyresis by acting centrally on the hypothalamic heat-regulating centre to produce peripheral vasolidation resulting in increased cutaneous blood flow, sweating and heat loss.

Paracetamol

Mechanism of action/effect

Analgesic – the mechanism of analgesic action has not been fully determined. Paracetamol may act predominantly by inhibiting prostaglandin synthesis in the central nervous system (CNS) and, to a lesser extent, through a peripheral action by blocking pain-impulse generation.

The peripheral action may also be due to inhibition of prostaglandin synthesis or to inhibition of the synthesis or actions of other substances that sensitise pain receptors to mechanical or chemical stimulation.

Antipyretic – paracetamol probably produces antipyresis by acting centrally on the hypothalamic heat-regulation centre to produce peripheral vasodilation resulting in increased blood flow through the skin, sweating, and heat loss. The central action probably involved inhibition of prostaglandin synthesis in the hypothalamus.

Caffeine

Mechanisms of action/effect

Central nervous system stimulant – caffeine stimulates all levels of the CNS, although its cortical effects are milder and of shorter duration than those of amphetamines.

Analgesia adjunct

Caffeine constricts cerebral vasculature with an accompanying decrease in the cerebral blood flow and in the oxygen tension of the brain. It is believed that caffeine helps to relieve headache by providing more rapid onset of action and/or enhanced pain relief with lower doses of analgesic. Recent studies with ergotamine indicate that the enhancement of effect by the addition of caffeine may also be due to improved gastrointestinal absorption of ergotamine when administered with caffeine.

5.2 Pharmacokinetic properties

Acetylsalicylic acid

Absorption and fate

Absorption is generally rapid and complete following oral administration. It is largely hydrolysed in the gastrointestinal tract, liver and blood to salicylate, which is further metabolised primarily in the liver.

Paracetamol

Absorption and fate

Paracetamol is readily absorbed from the gastro-intestinal tract with peak plasma concentrations occurring about 30 minutes to 2 hours after ingestion. It is metabolised in the liver and excreted in the urine mainly as the glucuronide and sulphate conjugates. Less than 5% is excreted as unchanged paracetamol. The elimination half-life varies from about 1 to 4 hours. Plasma-protein binding is negligible at usual therapeutic concentrations but increases with increasing concentrations.

A minor hydroxylated metabolite, which is usually produced in very small amounts by mixed-function oxidases in the liver, and which is usually detoxified by conjugation with liver glutathione may accumulate following paracetamol overdosage and cause liver damage.

Caffeine

Absorption and fate

Caffeine is completely and rapidly absorbed after oral administration with peak concentrations occurring between 5 and 90 minutes after dose in fasted subjects. There is no evidence of presystemic metabolism. Elimination is almost entirely by hepatic metabolism in adults.

In adults, marked individual variability in the rate of elimination occurs. The mean plasma elimination half-life is 4.9 hours with a range of 1.9 - 12.2 hours. Caffeine distributes into all body fluids. The mean plasma protein binding of caffeine is 35%.

Caffeine is metabolised almost completely via oxidation, demethylation, and acetylation, and is excreted in the urine as 1-methyluric acid, 1-methylxanthine, 7-methylxanthine, 1,7-dimethylxanthine (paraxanthine). Minor metabolites include 1-methylacrylic acid and 5-acethylamine-6-formylamine-3-methyluracil (AFMU).

5.3. Preclinical safety data

The active ingredients in TOPIRIN tablets have a well established safety record. This combination of ingredients has been marketed for a number of years.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Excipients:

- lactose monohydrate,
- pregelatinized starch,
- croscarmellose sodium,
- copovidone,
- colloidal silicon dioxide,
- stearic acid

6.2. Incompatibilities

No major incompatibilities have been noted.

6.3. Shelf life

3 years.

6.4. Special precautions for storage

TOPIRIN tablets store below 30°C in original packaging, out of reach of children!
There are no special requirements for storage.

6.5. Nature and contents of container

Carton box with 10 tablets of (250+250+50) mg in the blister pack.
Carton box with 20 tablets of (250+250+50) mg in the blister pack.

6.6. Special precautions for disposal and other handling

The procedure of unused drugs and waste materials derived from these drugs is carried out according to the regulations for the handling and disposal of pharmaceutical waste.

7. MARKETING AUTHORIZATION HOLDER

ZADA Pharmaceuticals Ltd.,
Donji Bistarac without number
75300 Lukavac,
Bosnia and Herzegovina

8. MARKETING AUTHORIZATION NUMBER(S)

Topirin, tablets 10x(250mg+250mg+50mg): 04-07.3-2-1719/18
Topirin, tablets 20x(250mg+250mg+50mg): 04-07.3-2-1718/18

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Topirin, tablets 10x(250mg+250mg+50mg): 01.11.2018.
Topirin, tablets 20x(250mg+250mg+50mg): 01.11.2018.

10. DATA OF LAST / PARTIAL REVISION OF THE TEXT

April,2015.