1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

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1. NAME OF THE MEDICINE

TRIPARC

TRIPARC BLACKCURRANT

TRIPARC ORANGE

TRIPARC LEMON

453,6 mg/ 324,00 mg/ 64,80 mg powders

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sachet of TRIPARC powder contains 453,6 mg aspirin, 324,00 mg paracetamol and 64,80 mg caffeine.

TRIPARC

Sugar free

TRIPARC BLACKCURRANT

Sugar free

Contains sweetener: Sucralose 37,80 mg

TRIPARC ORANGE

Sugar free

Contains sweetener: Sucralose 37,80 mg

TRIPARC LEMON

Sugar free

Contains sweetener: Sucralose 21,06 mg

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powders

TRIPARC is a fine white to off-white granular powder, free from rigid cakes or lumps.

TRIPARC BLACKCURRANT is a fine white to off-white granular powder with a sweet blackcurrant odour and taste, free from rigid cakes or lumps.

TRIPARC ORANGE is a fine white to off-white granular powder with a sweet orange odour and taste, free from rigid cakes or lumps.

TRIPARC LEMON is a fine white to off-white granular powder with a sweet lemon odour, free from rigid cakes or lumps.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

TRIPARC is indicated for:

- The symptomatic relief of mild to moderate pain and fever such as headaches, toothache, colds and flu.

4.2 Posology and method of administration

Posology

Do not exceed the stated dose.

Use the lowest effective dose for the shortest possible duration of treatment.

Adults

One powder to be taken with water every three hours.

Do not use more than one powder every 3 to 4 hours if necessary and not more than 6 powders during a 24-hour period.

Maximum daily dose: 6 powder sachets

Minimum dosing interval: 3 hours

Should not be taken with other paracetamol or aspirin containing medicines (see section 4.5).

Paediatric population

No data are available (see sections 4.3 and 4.4).

Method of administration

For oral administration.

Powder to be taken with water.

4.3 Contraindications

TRIPARC is contraindicated in:

- Patients with hypersensitivity to aspirin, paracetamol, caffeine or to any excipients in TRIPARC (see section 6.1).

- Patients in whom asthma, bronchospasm, angioedema, urticaria, or acute rhinitis are precipitated by aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs).
- Patients with a history of upper gastrointestinal perforation, ulceration or bleeding (PUBs) related to previous therapy with NSAIDs.
- Patients with active or a history of recurrent ulcer/haemorrhage/perforations.
- Patients with a history of haemophilia, hypothrombinaemia or other clotting disorders.
- Patients with renal failure.
- Patients with hepatic failure.
- Patients receiving oral anti-coagulant therapy (warfarin) (see section 4.5).
- Patients with heart failure.
- Lactation (see section 4.6).
- Patients with a history of gout.
- Pregnant women in their third trimester of pregnancy (see section 4.4 and 4.6).
- Patients under the age of 12 years (see section 4.4).

4.4 Special warnings and precautions for use

TRIPARC contains paracetamol which may be fatal in overdose. In the event of overdosage and notwithstanding the fact that the person may be asymptomatic, the nearest doctor, hospital or Poison Control Centre must be contacted immediately.

DO NOT EXCEED THE RECOMMENDED DAILY DOSE.

Dosages in excess of those recommended may cause severe liver damage.

Do not use continuously for more than 10 days without consulting your doctor.

Medical advice should be sought if cough persists, or if it is accompanied by high fever, skin rash or persistent headache.

The use of NSAIDs around 20 weeks gestation or later in pregnancy may cause rare but serious foetal renal dysfunction leading to oligohydramnios and, in some cases constriction of the ductus arteriosus (see section 4.6).

Aspirin

Aspirin, as in TRIPARC, should be administered with caution to patients with impaired renal or hepatic function, dyspepsia, anaemia and when the patient is dehydrated, or suffering from diabetes mellitus. Prolonged use of high doses may lead to anaemia, blood dyscrasias, gastrointestinal haemorrhage, peptic ulceration, renal papillary necrosis and in the presence of uncontrolled hypertension.

There is an association between aspirin, as in TRIPARC, and Reye's syndrome when given to children and teenagers during or immediately after a viral illness (such as chickenpox and influenza). Reye's syndrome is a rare disease which affects the brain and liver and can be fatal. For this reason, children and teenagers (between 12 and 16 years of age) who have or are recovering from chicken pox or flu-like symptoms should not use this medicine, unless prescribed by a healthcare practitioner (see section 4.3). When using this medicine, if changes in behaviour with nausea and vomiting occur, the patient should consult a doctor because these symptoms could be an early sign of Reye's syndrome, a rare but serious illness.
A doctor should be consulted before TRIPARC is used in such patients.

Concomitant use of aspirin, as in TRIPARC, with other systemic NSAID's including cyclooxygenase-2-seletive inhibitors, should be avoided due to the potential for additive undesirable effects (see section 4.5).

Serious hypersensitivity reactions or anaphylaxis can occur, bronchospasm may be precipitated in patients suffering from or with previous history of asthma, allergic disease or nasal polyps.

Caution is required in patients with a history of hypertension and/or heart failure as fluid retention and oedema have been reported in association with therapy with aspirin as in TRIPARC.

In view of the medicine's inherent potential to cause fluid retention, heart failure may be precipitated in some compromised patients.

The risk of PUBs is higher with increasing doses of TRIPARC, in patients with a history of ulcers, and the elderly (see section 4.3).

Gastrointestinal bleeding, ulceration or perforation, which can be fatal have been reported with all NSAID's and may occur at any time during treatment, with or without warning symptoms or a previous history of serious gastrointestinal events.
When gastrointestinal bleeding or ulceration occurs in patients receiving TRIPARC, treatment with TRIPARC should be stopped.

TRIPARC should be given with caution to patients with history of gastrointestinal disease (e.g. ulcerative colitis. Crohn's disease, hiatus hernia, gastro-oesophageal reflux disease, dyspepsia, angiodysplasia) as the condition may be exacerbated.
Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN) have been reported. TRIPARC should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Drug reaction with eosinophillia and systemic symptoms (DRESS) has been reported in patients taking NSAIDs containing medicines such as TRIPARC. Some of these events have been fatal or life-threatening. DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling. Other clinical manifestations may include hepatitis, nephritis, haematological abnormalities, myocarditis, or myositis. Sometimes symptoms of DRESS may resemble an acute viral infection. Eosinophillia is often present. Because this disorder is variable in its presentation, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, discontinue TRIPARC and evaluate the patient immediately.

Aspirin, as in TRIPARC, 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 healthcare practitioner. Due to its inhibitory effect on platelet aggregation aspirin may cause increased bleeding during and after surgery. As TRIPARC contains aspirin, treatment should be discontinued several days before scheduled surgical procedures.

The use of TRIPARC in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency may lead to haemolytic anaemia as more than 1 g aspirin daily may precipitate acute haemolytic anaemia in patients with G6PDH deficiency.

Long term use of TRIPARC may cause iron-deficiency anaemia.

Aspirin as in TRIPARC may interfere with insulin and glucagon control in diabetics.

Aspirin as in TRIPARC can interfere with thyroid function tests.

Persons sensitive to aspirin as in TRIPARC, often have cross-sensitivity to NSAIDs. Some patients, especially those with asthma, chronic urticaria or chronic rhinitis, exhibit notable hypersensitivity to aspirin, which may provoke reactions including urticaria, angioedema, rhinitis and severe even fatal paroxysmal bronchospasm and dyspnoea.

Elderly: The elderly have an increased frequency of adverse reactions to NSAIDs, including TRIPARC, especially gastrointestinal bleeding and perforation (PUBs), which may be fatal. The risk of gastrointestinal bleeding or perforation (PUBs) is higher with increasing doses of TRIPARC, in patients with a history of ulcers, and the elderly.

Pregnancy:

Regular use of NSAIDs such as TRIPARC during the third trimester of pregnancy, may result in premature closure of the foetal ductus arteriosus *in utero*, and possibly, in persistent pulmonary hypertension of the new-born. The onset of labour may be delayed and its duration increased (see section 4.6).

The use of NSAIDs, such as aspirin, as in TRIPARC, around 20 weeks gestation or later in pregnancy may cause foetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. Oligohydramnios is often, but not always, reversible with treatment discontinuation. Complications of prolonged oligohydramnios may include limb contractures and delayed lung maturation. In some postmarketing cases of impaired neonatal renal function, invasive procedures such as exchange transfusion or dialysis were required.

Healthcare professionals should consider ultrasound monitoring of amniotic fluid if TRIPARC treatment extends beyond 48 hours. Discontinue TRIPARC if oligohydramnios occurs and follow up according to clinical practice.

Paracetamol

TRIPARC contains paracetamol. Do not use with any other paracetamol containing medicines. Concomitant use with other medicines containing paracetamol may lead to an overdose. Paracetamol overdose may cause liver failure which may require liver transplant or lead to death.

The hazards of overdose are greater in those with non-cirrhotic alcoholic liver disease.

Patients suffering from hepatic or renal disease should take paracetamol under medical supervision.

Underlying liver disease increases the risk of paracetamol related liver damage. The overall benefit-risk should be considered in patients diagnosed with liver or kidney impairment before use.

Cases of hepatic failure have been reported in patients with depleted glutathione levels, such as 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 as in TRIPARC may increase the risk of metabolic acidosis.

Paracetamol as in TRIPARC, should also be given with care to patients with alcohol dependence, chronic malnutrition, or dehydration.

Severe cutaneous adverse reactions (SCARs) such as toxic epidermal necrolysis (TEN), exfoliative dermatitis, Steven-Johnson syndrome (SJS), acute generalized exanthematous pustulosis (AGEP), eosinophilia and systemic (DRESS)/Drug-induced hypersensitivity syndrome (DIHS) and fixed drug eruptions (FDE) have been reported in patients treated with paracetamol containing medicines, as contained in TRIPARC. If a patient develops SCAR, skin rash, mucosal lesions or other signs of hypersensitivity, treatment with TRIPARC must immediately be discontinued and appropriate treatment instituted.

Caffeine

Excess intake of caffeine (e.g. tea, coffee and some canned drinks) should be avoided while taking TRIPARC.

Paediatric population

TRIPARC should not be used in children under the age of 12 (see section 4.3). There is an association between aspirin and Reye's syndrome when given to children and teenagers during or immediately after a viral illness (such as chickenpox and influenza). Reye's syndrome is a rare disease which affects the brain and liver and can be fatal. For this reason, children and teenagers (between 12 and 16 years of age) who have or are recovering from chickenpox or flu-like symptoms should not use this medicine, unless prescribed by a health practitioner (see section 4.3).

4.5 Interaction with other medicines and other forms of interaction

Aspirin, paracetamol and caffeine combination medicines, such as TRIPARC, should not be used together with other non-steroidal anti-inflammatory drugs (NSAIDs) including acetylsalicylic acid and cyclo-oxygenase-2-specific inhibitors as these may increase the risk of adverse effects. Aspirin, paracetamol and caffeine combination medicines should be used

with caution when taken in combination with the following medicines as interactions have been reported.

Aspirin

Other NSAIDS

Use of two or more NSAIDs concomitantly could result in an increase in undesirable effects.

Corticosteroids: Concurrent use of other NSAIDs or corticosteroids may increase the likelihood of GI side effects including perforation, ulceration and bleeding (PUB). Aspirin as in TRIPARC may decrease the plasma concentration of some other NSAIDs, for example, indomethacin, and piroxicam.

Diuretics: Antagonism of the diuretic effect. There is a risk of a reduced diuretic effect especially in patients with existing renal or cardiovascular disease.

Beta-blockers: Aspirin, as in TRIPARC, can reduce antihypertensive effect of beta-blockers.

Anticoagulants such as warfarin and platelet aggregation inhibitors:

TRIPARC may enhance the effects of anticoagulants such as coumarins (e.g. warfarin) and heparin, and of platelet aggregation inhibitors such as ticlopidine, clopidogrel, and cilostazol, as there is an increased risk of bleeding. Clinical and laboratory monitoring of the bleeding time and prothrombin time should be performed.

Thrombolytics: There is an increased risk of bleeding. Particularly treatment with TRIPARC should not be initiated within the first 24 hours after treatment with alteplase in acute stroke patients. Concomitant use is therefore not recommended.

Uricosurics: Aspirin, as in TRIPARC diminishes the effects of antigout preparations such as probenecid and sulphinpyrazone, due to inhibition of tubular resorption, leading to high plasma levels of aspirin.

Loop diuretics (e.g. furosemide): Aspirin, as in TRIPARC, may reduce their activity due to competition and inhibition of urinary prostaglandins. NSAIDs can cause acute kidney failure, especially in dehydrated patients. If a diuretic is administered simultaneously with aspirin, as in TRIPARC, it is necessary to ensure adequate hydration of the patient to monitor the kidney function and blood pressure, particularly when starting diuretic treatment.

Metoclopramide: Metoclopramide increases the rate of absorption of aspirin, as in TRIPARC. However, concurrent use need not be avoided.

Phenytoin: The effect of phenytoin may be enhanced by aspirin, as in TRIPARC. Aspirin increases serum levels of phenytoin. Serum phenytoin should be well monitored.

Valproate: The effect of valproate may be enhanced by aspirin, as in TRIPARC. Aspirin inhibits its metabolism and hence could increase its toxicity Valproate levels should be well monitored.

Methotrexate (≤15 mg/ week): Delayed excretion and increased toxicity of methotrexate. In case of concomitant use with TRIPARC, renal function should be monitored.

Alcohol: Some of the side effects of aspirin, as in TRIPARC, on the gastrointestinal tract are enhanced by alcohol. Co-administration of alcohol and aspirin increases the risk of gastrointestinal haemorrhage.

Gold compounds: Use of gold compounds with aspirin, as in TRIPARC may exacerbate aspirin-induced liver damage.

Dipyridamole: Use of aspirin, as in TRIPARC, with dipyridamole may result in an increase in plasma-salicylate concentrations.

Metoprolol: May also increase peak plasma-salicylate concentrations.

Diuretics and antihypertensive medicines: Concomitant use of aspirin with diuretics or antihypertensive medicines (e.g. beta blockers, angiotensin converting enzyme (ACE) inhibitors) may cause a decrease in their antihypertensive effect. Therefore, the combination should be administered with caution and patients, especially the elderly, should have their blood pressure periodically monitored. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy and periodically thereafter, particularly for diuretics and ACE inhibitors, due to the increased risk of nephrotoxicity. Concomitant treatment with potassium-sparing medicines may be associated with increased serum potassium levels, which should therefore be monitored frequently.

Carbonic anhydrase inhibitors: Salicylate intoxication has occurred in patients on high-dose salicylate regimens (aspirin as in TRIPARC) and carbonic anhydrase inhibitors.

Antacids: Antacids may increase the excretion of aspirin by alkalinisation of urine.

Sulphonylureas: Aspirin, as in TRIPARC, may enhance the activity of oral antidiabetic medicines and sulphonamides, thus some downward readjustment of the dosage of the

antidiabetic may be appropriate if large doses of salicylates are used. Increased blood glucose controls are recommended.
Aspirin, as in TRIPARC, may increase the activity of sulfonylurea hypoglycaemic medication and zafirlukast.

Aspirin, as in TRIPARC, diminishes the effects of uricosurics such as probenecid and sulfinpyrazone.

Barbiturates and other sedatives: May mask the respiratory symptoms of aspirin, as in TRIPARC, overdosage and have been reported to enhance its toxicity.

Anti-platelet medicines and selective serotonin reuptake inhibitors (SSRIs): Increase risk of gastrointestinal bleeding.

Paracetamol

Alcohol: Reduces the liver's capacity to deal with paracetamol.

Cholestyramine: The speed of absorption of paracetamol, as in TRIPARC, is reduced by cholestyramine. Therefore, the cholestyramine should not be taken within one hour if maximal analgesia is required.

Metoclopramide and domperidone: The speed of absorption of paracetamol as in TRIPARC is increased by metoclopramide and domperidone. However, concurrent use need not be avoided.

Warfarin: The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular use of paracetamol, as in TRIPARC, with increased risk of bleeding; occasional doses have no significant effect.

Chloramphenicol: Increased plasma concentration of chloramphenicol.

The risk of paracetamol toxicity may be increased in patients receiving other potentially hepatotoxic medications or medications that induce liver microsomal enzymes.

Probenecid: Excretion may be affected and plasma concentrations altered when paracetamol as in TRIPARC is given with probenecid.

Caffeine

Antibacterials (ciprofloxacin and pipemidic acid): Caffeine elimination half-life has been reported to be increased and clearance decreased.

Antidepressants (fluvoxamine): Fluvoxamine reduces the clearance and prolongs the elimination half-life of caffeine, as in TRIPARC.

Antiepileptics (phenytoin): The mean clearance of caffeine was increased and its half-life decreased in epileptic patients taking phenytoin, resulting in lower plasma-caffeine concentrations.

Antigout medicines (allopurinol): Allopurinol caused a dose-dependent inhibition of the conversion of 1-methylxanthine to 1-methyluric acid.

Gastrointestinal medicines (cimetidine): Oral cimetidine reduced the systemic clearance of caffeine, as in TRIPARC, and prolonged its elimination half-life in healthy patients.

Methoxsalen: Methoxsalen reduced the clearance of caffeine, as in TRIPARC, in patients with psoriasis, consistent with a cytochrome P450 isoenzyme CYP1A2-dependant inhibition of caffeine demethylation.

Oral contraceptives and hormone replacement therapy: The clearance of caffeine, as in TRIPARC, has been reported to be reduced and its elimination half-life increased in women taking oral contraceptives as well as postmenopausal women given oestrogens for hormone replacement therapy.

Lithium: Caffeine can increase the elimination of lithium from the body, concomitant use is therefore not recommended.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of TRIPARC in pregnancy and lactation has not been established. TRIPARC is not recommended for use during pregnancy and is contraindicated during the third trimester of pregnancy (see section 4.3).

Pregnant women should seek medical advice before taking TRIPARC.

Aspirin, as in TRIPARC, should be avoided in the first two trimesters of pregnancy unless the potential benefit to the mother outweighs the risk to the foetus in the view of the treating physician. Regular use of NSAIDs such as TRIPARC during the third trimester of pregnancy, may result in premature closure of the foetal ductus arteriosus in utero, and possibly, in persistent pulmonary hypertension of the new-born and a risk of foetal renal impairment with subsequent oligohydramnios.

The onset of labour may be delayed and its duration increased, with increased risk of bleeding tendency in both the mother and child. If the expected benefit to the mother is greater than the possible risk to the foetus, the lowest effective dose and the shortest duration of treatment should be considered.

Caffeine is not recommended for use during pregnancy due to the possible increased risk of spontaneous abortion associated with caffeine consumption.

Breastfeeding

TRIPARC is not recommended for use during breastfeeding.

There is insufficient information on the effects of aspirin at low concentration in infants (see section 4.3).

Aspirin, as in TRIPARC, is secreted into breast milk in low concentrations, and regular high doses may affect neonatal clotting.

Treatment should be avoided during breastfeeding because of the possible risk of Reye's syndrome and the potential impairment of platelet function in the infant, as well as neonatal bleeding due to hypoprothrombinaemia.

Paracetamol, as in TRIPARC, is excreted in breastmilk but not in a significant amount at recommended dosages.

Caffeine, as in TRIPARC, appears in breast milk. Caffeine in breastmilk may potentially have a stimulating effect on breast fed infants but significant toxicity has not been observed. Irritability and poor sleeping pattern in the infant can occur.

Fertility

There is no fertility data.

4.7 Effects on ability to drive and use machines

TRIPARC has a no or negligible influence on the ability to drive and use machines.

Since adverse reactions such as dizziness, headache and vertigo have been reported in patients receiving TRIPARC, patients should not drive, use machinery or perform any tasks that require concentration, until they are certain that TRIPARC does not adversely affect their ability to do so (see section 4.4 and/or 4.8).

4.8 Undesirable effects

a) Tabulated list of adverse reactions

Paracetamol

System organ class	**Less frequent**	**Frequency unknown** (cannot be estimated from the available data)
Blood and the lymphatic system disorders	Haematological reactions including thrombocytopenia, leucopenia, pancytopenia, neutropenia, agranulocytosis	
Immune system disorders		Anaphylaxis, cutaneous hypersensitivity reactions including rashes, angioedema
Respiratory, thoracic and mediastinal disorders		Bronchospasm*[1]
Gastrointestinal disorders	Pancreatitis, nausea, vomiting	
Hepato-biliary disorders	Hepatitis, hepatic necrosis, increased levels of transaminases, hepatic failure	
Skin and subcutaneous tissue disorders	Dermatitis, skin rashes, other hypersensitivity reactions[2]	Severe cutaneous adverse reactions (SCARs) such as Stevens Johnson syndrome/toxic epidermal necrolysis, acute generalised exanthematous pustulosis (AGEP), eosinophilia and systemic (DRESS)/Drug-induced hypersensitivity syndrome (DIHS), fixed drug eruption (FDE) (see section4.4)*
Renal and urinary disorders	Renal colic, renal failure and sterile pyuria	

** Post marketing data*
[1]There have been cases of bronchospasm with paracetamol, but these are more likely in asthmatics sensitive to aspirin or other NSAIDs
[2] The rash is usually erythematous or urticarial but sometimes more serious and may be accompanied by fever and mucosal lesions

Aspirin

System organ class	Frequent	Less frequent	Frequency unknown (cannot be estimated from the available data)
Blood and the lymphatic system disorders		Prolonged use of high doses may lead to iron-deficiency anaemia, blood dyscrasias, gastrointestinal haemorrhage[1]	Prolonged bleeding time, thrombocytopenia, ecchymosis
Immune system disorders			Hypersensitivity reactions including, anaphylaxis angioedema, severe bronchoconstriction, paroxysmal bronchospasm, dyspnoea, skin eruptions (especially in persons with asthma, chronic urticaria and rhinitis)
Metabolism and nutrition disorders			Sodium and fluid retention
Nervous system disorders			Mental confusion, dizziness
Ear and labyrinth disorders			Hearing disturbances (such as tinnitus), vertigo, temporary hearing loss
Cardiac disorders			Oedema, cardiac failure
Vascular disorders			Hypertension
Respiratory, thoracic and mediastinal disorders	Rhinitis[2]		Bronchospasm in patients sensitive to aspirin and other NSAIDs
Gastrointestinal disorders[3]	Nausea, vomiting, diarrhoea, flatulence, dyspepsia		Peptic ulcers, perforation, peptic ulceration and gastrointestinal bleeding (PUBs), sometimes fatal, constipation, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis, Crohn's disease, gastritis
Hepato-biliary disorders			Reye's Syndrome (in children under 16), elevation in transaminase levels

Skin and subcutaneous tissue disorders		Urticaria, other skin eruptions, skin reactions	Skin eruptions, bullous reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis, Drug Reaction with Eosinophillia and Systemic Symptoms (DRESS) (see section 4.4)
Renal and urinary disorders		Renal papillary necrosis	Renal dysfunction, increased blood uric acid levels
Reproductive system and breast disorders			Prolonged pregnancy and labour, peripartum bleeding

[1]Prolonged bleeding time, and bleeding disorders, such as epistaxis, purpura and intracranial haemorrhage may occur.

[2] Some persons especially asthmatics, exhibit notable sensitivity to aspirin which may provoke various hypersensitivity reactions which may include skin eruptions, paroxysmal bronchospasm and dyspnoea. Worsening of asthma may occur

Caffeine

System organ class	**Frequent**	**Less frequent**	**Frequency unknown** (cannot be estimated from the available data)
Psychiatric disorders			Insomnia, restlessness, anxiety and irritability, nervousness
Nervous system disorders		Stimulation of the central nervous system with anxiety, restlessness, vertigo, tremor (high doses)	Headache, dizziness
Cardiac disorders			Palpitation (high doses)
Gastrointestinal disorders	Gastrointestinal irritation with vomiting, abdominal pain	Gastrointestinal bleeding	Nausea, increased gastric secretions, may cause gastric ulceration, gastrointestinal disturbances

b) Description of selected adverse reactions

When the recommended aspirin-caffeine dosing regimen is combined with dietary caffeine intake, the resulting higher dose of caffeine may increase the potential for caffeine- related adverse effects such as insomnia, restlessness, anxiety, irritability, headaches, gastrointestinal disturbances and palpitations.

Caffeine increases gastric secretions and may cause gastric ulceration.
Adverse events due to caffeine are more likely to occur with increasing dose and duration of use.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to:

SAHPRA: https://www.sahpra.org.za/Publications/Index/8

Aspen Pharmacare:

E-mail: Drugsafety@aspenpharma.com

Tel: 0800 118 088

4.9 Overdose

Immediate medical management is required in the event of overdose, even if symptoms of overdose are not present. If overdose is confirmed or suspected, seek immediate advice from your Poison Control Centre and refer patient to nearest Emergency Medical Centre for management and expert treatment. This should happen even in patients without symptoms or signs of overdose due to the risk of delayed liver damage.

Aspirin:

Symptoms

Mild chronic salicylate intoxication, or salicylism, usually occurs only after repeated use of large doses. Salicylism can also occur following excessive topical application of salicylates. Symptoms include dizziness, tinnitus, deafness, sweating, nausea and vomiting, headache and confusion, vertigo, deafness, sweating, mental confusion, dehydration, increased

respiratory rate, hyperventilation, warm extremities with bounding pulses, respiratory alkalosis, metabolic acidosis, ketosis and depression of the central nervous system and may be controlled by reducing the dosage. Tinnitus can occur at the plasma concentrations of 150 to 300 micrograms/ml required for optimal anti-inflammatory activity; more serious adverse effects occur at concentrations above 300 micrograms/ml.

Depression of the CNS may lead to coma; cardiovascular collapse and respiratory failure may also occur. In children drowsiness and metabolic acidosis commonly occur; hypoglycaemia may be severe.

In children serious signs of overdosage may develop rapidly.
Uncommon features include haematemesis, hyperpyrexia, hypoglycaemia, hypokalaemia, thrombocytopaenia, increased INR/ PTR, intravascular coagulation, renal failure and noncardiac pulmonary oedema. Central nervous system features including confusion, disorientation, coma and convulsions are less common in adults than in children.

Treatment

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

Paracetamol:

Prompt treatment is essential even when there are no obvious symptoms. In the event of an overdosage, consult a doctor immediately, or take the person directly to hospital. A delay in starting treatment may mean that antidote is given too late to be effective. Evidence of liver damage is often delayed until after the time for effective treatment has lapsed.

Susceptibility to paracetamol toxicity is increased in patients who have taken repeated high doses (greater than 5 to10 g/day) of paracetamol for several days, in chronic alcoholism, chronic liver disease, AIDS, malnutrition, fasting and with the use of medicines that induce liver microsomal oxidation such as barbiturates, isoniazid, rifampicin, phenytoin and carbamazepine.

Symptoms

Symptoms of paracetamol overdosage in the first 24 hours include pallor, nausea, vomiting, anorexia and abdominal pain may persist for a week or more. Cerebral oedema and nonspecific myocardial depression have also occurred. Mild symptoms during the first two days of acute poisoning, do not reflect the seriousness of the overdosage.

Liver damage may become apparent 12 to 48 hours or later after ingestion, initially by elevation of the serum transaminase and lactic dehydrogenase activity, metabolic acidosis, increased serum bilirubin concentration and prolongation of the prothrombin time/INR failure. Liver damage may lead to encephalopathy, coma and death.

Acute renal failure with acute tubular necrosis may develop even in the absence of severe liver damage. Abnormalities of glucose metabolism and metabolic acidosis may occur. Cardiac dysrhythmias have been reported.
In the event of overdosage consult a doctor or take the patient to the nearest hospital immediately. Specialised treatment is essential as soon as possible. Any patient who has ingested about 7,5 g of paracetamol in the preceding 4 hours should undergo gastric lavage. Specialised therapy with an antidote such as N-acetylcysteine or methionine may be necessary. If decided upon, N-acetylcysteine should be administered IV as soon as possible.

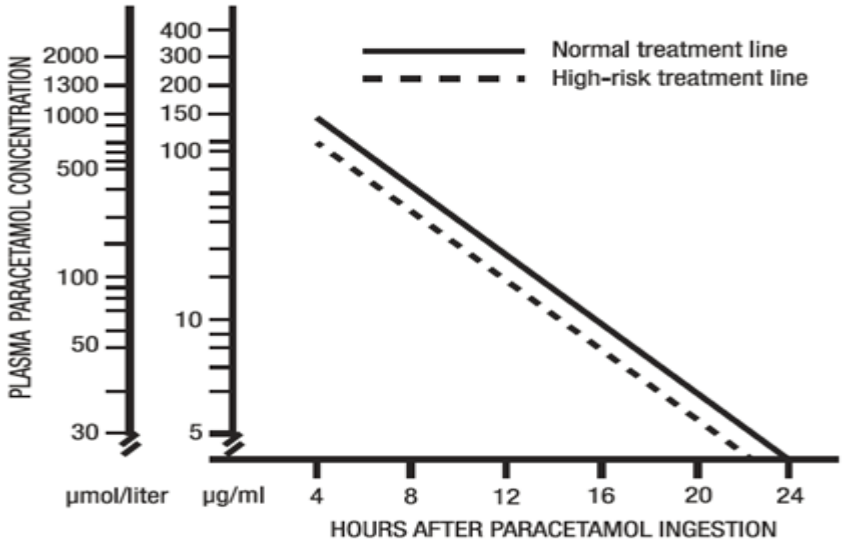
Treatment of paracetamol overdosage:
Immediate hospitalisation is crucial. A single dose of 50 g activated charcoal given via the lavage tube. Ingestion of amounts of paracetamol smaller than this may require treatment in patients susceptible to paracetamol poisoning (see above).

N-acetylcysteine should be administered to all cases of suspected overdose as soon as possible preferably within eight hours of overdosage, although treatment up to 36 hours after ingestion may still be of benefit, especially if more than 150 mg/kg of paracetamol was taken.
IV: An initial dose of 150 mg/kg N-acetylcysteine in 200 ml glucose (5 % w/v) intravenous injection, given intravenously over 15 minutes, followed by an infusion of 50 mg/kg in 500 ml glucose (5 % w/v) injection over the next four hours, and then 100 mg/kg in 1 000 ml over

the next sixteen hours. Sodium chloride 0,9 % w/v may be used where glucose 5 % w/v is not suitable. The volume of intravenous fluid should be modified for children.

Orally: Although the oral formulation is not treatment of choice, 140 mg/kg may be administered as a 5 % solution, may be administered initially, followed by 70 mg/kg every four hours for seventeen doses. N-acetylcysteine is effective if administered within 8 hours of overdosage.

A plasma paracetamol level should be determined four hours after ingestion in all cases of suspected overdosage. Levels done before four hours may be misleading. Patients at risk of liver damage, and hence requiring continued treatment with N-acetylcysteine, can be identified according to their 4-hour plasma paracetamol level. The plasma paracetamol level can be plotted against time since ingestion in the nomogram below. The nomogram should be used only in relation to a single acute ingestion.



Those, whose plasma paracetamol levels are above the “Normal treatment line”, should continue N-acetylcysteine treatment with 100 mg/kg IV over sixteen hours repeatedly until

recovery. Patients with increased susceptibility to liver damage as identified above, should continue treatment if concentrations are above the “High-risk treatment line”. Prothrombin index/INR correlates best with survival.

Monitor all patients with significant ingestions for at least ninety-six hours.

Caffeine

Symptoms

Large doses may cause restlessness, CNS stimulation, nervousness, insomnia, confusion, excitement, muscle tremor, tinnitus, scintillating scotoma, tachycardia, extrasystoles, epigastric pain, vomiting, diuresis, cardiac dysrhythmia, agitation, anxiety and convulsions.

Treatment

Treatment is symptomatic and supportive. In the event of overdosage consult a doctor or take the patient to the nearest hospital immediately. Specialised treatment is essential as soon as possible.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and Class: A 2.8 Analgesic Combinations

Pharmacotherapeutic group: Other analgesics and antipyretics

ATC code: N02BA

Mechanism of action

The combination of aspirin, paracetamol and caffeine has analgesic, antipyretic and anti-inflammatory properties.

Aspirin has analgesic, antipyretic and anti-inflammatory properties. It inhibits the biosynthesis of prostaglandins, and produces analgesia through peripheral action by blocking pain impulse generation as well as by a central action.

Paracetamol has analgesic and antipyretic properties. It acts predominantly by inhibiting prostaglandin synthesis.

Caffeine has central nervous system stimulating effects.

5.2 Pharmacokinetic properties

Paracetamol

Absorption

Paracetamol has excellent bioavailability. Peak plasma concentrations occur within 30 to 60 minutes, and the t½ in plasma is ~ 2 hours after therapeutic doses.

Distribution

Paracetamol is relatively uniformly distributed throughout most body fluids. Binding of paracetamol to plasma proteins is variable.

Biotransformation

Paracetamol primarily undergoes hepatic conjugation with glucuronic acid (~ 60 %), sulphuric acid (~ 35 %) or cysteine (~ 3 %). Small amounts of the hydroxylated and deacetylated metabolites have also been detected. A small proportion of paracetamol undergoes CYP-mediated N-hydroxylation to form NAPQI, a highly reactive intermediate. This metabolite normally reacts with sulphydryl groups in glutathione (GSH) and thereby is rendered harmless. However, after ingestion of large doses of paracetamol, the metabolite is

formed in amounts sufficient to deplete hepatic GSH and contributes significantly to the toxic effects of overdose.

Elimination

Some 90 to 100 % of paracetamol may be recovered in the urine within the first day of therapeutic dosing.

Aspirin

Absorption

Orally ingested salicylates are absorbed rapidly, partly from the stomach but mostly from the upper small intestine. Appreciable concentrations are found in plasma in < 30 minutes; after a single dose, a peak value is reached in ~ 1 hour and then declines gradually. The rate of absorption is determined by many factors, particularly the disintegration and dissolution rates of the tablets administered, the pH at the mucosal surface, and gastric emptying time.

Distribution

After absorption, salicylates are distributed throughout most body tissues and transcellular fluids, primarily by pH-dependent passive processes. Salicylates are transported actively by a low-capacity, saturable system out of the cerebrospinal fluid (CSF) across the choroid plexus. The medication readily crosses the placental barrier.

The volume of distribution of usual doses of aspirin and sodium salicylate in normal subjects averages 170 ml/kg of body weight; at high therapeutic doses, this volume increases to 500 ml/kg because of saturation of binding sites on plasma proteins. Ingested aspirin mainly is absorbed as such, but some enters the systemic circulation as salicylic acid after hydrolysis by esterases in the GI mucosa and liver. Aspirin can be detected in the plasma only for a

short time as a result of hydrolysis in plasma, liver and erythrocytes; for example, 30 minutes after a dose of 0,65 g, only 27 % of the total plasma salicylate is in the acetylated form.

Roughly 80 to 90 % of the salicylate in plasma is bound to proteins, especially albumin, at concentrations encountered clinically; the proportion of the total that is bound declines as plasma concentrations increase.

Biotransformation

The biotransformation of salicylates takes place in many tissues, but particularly in the hepatic endoplasmic reticulum and mitochondria. The three chief metabolic products are salicylic acid (the glycine conjugate), the ether or phenolic glucuronide, and the ester or acyl glucuronide. In addition, a small fraction is oxidized to gentisic acid (2,5-dihydroxybenzoic acid) and to 2,3-dihydroxybenzoic and 2,3,5-trihydroxybenzoic acids; gentisuric acid, the glycine conjugate of gentisic acid, also is formed.

Elimination

Salicylates are excreted in the urine as free salicylic acid (10 %), salicyluric acid (75 %), salicylic phenolic (10 %) and acyl glucuronides (5 %), and gentisic acid (< 1 %). However, excretion of free salicylates is extremely variable and depends on the dose and the urinary pH.

The plasma t½ for aspirin is ~ 20 minutes, and for salicylate is 2 to 3 hours at antiplatelet doses, rising to 12 hours at usual anti-inflammatory doses.

Special populations

Elderly

Salicylate clearance is reduced and salicylate exposure is significantly increased in the elderly.

Renal impairment

The plasma concentration of salicylate is increased by conditions that decrease glomerular filtration rate or reduce proximal tubule secretion, such as renal disease or the presence of inhibitors that compete for the transport system.

Caffeine

Absorption

Caffeine is absorbed from the digestive tract.

Distribution

Caffeine is distributed rapidly throughout all tissues and easily crosses the placental barrier

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

TRIPARC: Colloidal anhydrous silica

TRIPARC BLACKCURRANT: Blackcurrant Flavour Permaseal, sucralose

TRIPARC ORANGE: Orange flavour, sucralose

TRIPARC LEMON: Colloidal anhydrous silica, Trusil Lemon Special, sucralose

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store in a cool, dry place at or below 30 °C. Keep well closed. Use the sachet immediately after opening. Do not remove the product from the carton until required for use.

6.5 Nature and contents of container

TRIPARC is packed in a sachet consisting of a white to off-white paper triple laminated with low-density polyethylene and aluminium foil or a white paper double laminated with low-density polyethylene. 12 or 38 sachets are packed into a unit cardboard carton together with a leaflet. Single doses are packed into a dispenser.

TRIPARC BLACKCURRANT and TRIPARC ORANGE are packed in a sachet consisting of a white paper triple laminated with low-density polyethylene and aluminium foil or a white paper triple laminated with low-density polyethylene and polyester. 10 or 24 sachets are packed into a unit cardboard carton together with a leaflet, and single sachets are packed into a dispenser.

TRIPARC LEMON is packed in a sachet consisting of a white to off-white paper triple laminated with low-density polyethylene and aluminium foil or a white paper triple laminated with low-density polyethylene and polyester. 12 sachets are packed into a unit cardboard carton together with a leaflet.

Not all packs and pack sizes are necessarily marketed.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead 2191

8. REGISTRATION NUMBER

TRIPARC	46/2.8/0139
TRIPARC BLACKCURRANT	46/2.8/0137
TRIPARC ORANGE	46/2.8/0138
TRIPARC LEMON	46/2.8/0140

9. DATE OF FIRST AUTHORISATION

29 July 2016

10. DATE OF REVISION OF TEXT

13 November 2023

Die Afrikaanse Professionele Inligting is op versoek beskikbaar. Mediese Blitslyn: 0800 118 088.

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