SCHEDULING STATUS: S0

PROPRIETARY NAME AND DOSAGE FORM:

GRAND-PA HEADACHE TABLETS

GRAND-PA HEADACHE POWDERS

COMPOSITION:

GRAND-PA HEADACHE TABLETS: Each tablet contains:

Aspirin ..... 226,8 mg

Paracetamol ..... 162,0 mg

Caffeine ..... 32,4 mg

Inactive ingredients: Colloidal silicon dioxide, microcrystalline cellulose and stearic acid. Sugar free.

GRAND-PA HEADACHE POWDERS: Each powder contains:

Aspirin ..... 453,6 mg

Paracetamol ..... 324,0 mg

Caffeine ..... 64,8 mg

Inactive ingredients: Magnesium stearate. Sugar free.

CATEGORY AND CLASS:

A 2.8. Analgesic combinations

PHARMACOLOGICAL ACTION:

GRAND-PA HEADACHE TABLETS and GRAND-PA HEADACHE POWDERS have analgesic, antipyretic and anti-inflammatory properties.

INDICATIONS:

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

CONTRA-INDICATIONS:

GRAND-PA is contraindicated in the following conditions:

- Hypersensitivity to aspirin, paracetamol, caffeine or to any of the excipients.
- Patients in whom asthma, bronchospasm, angioedema, urticaria, or acute rhinitis are precipitated by aspirin or other non-steroidal anti-inflammatory drugs (NSAID's)
- History of upper gastrointestinal bleeding or perforation, related to previous NSAID therapy, including GRAND PA.
- Active or history of recurrent ulcer/ haemorrhage / perforations.
- Heart failure
- History of haemophilia, hypothrombinaemia or other clotting disorders.
- Renal failure
- Hepatic failure
- A history of gout
- Third trimester of pregnancy.

WARNINGS AND SPECIAL PRECAUTIONS:

This product contains paracetamol which may be fatal in overdose. In 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.

Aspirin

Aspirin should be administered with caution to patients with uncontrolled hypertension, 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 and renal papillary necrosis.

There is an association between aspirin and Reye's syndrome when given to children during or immediately after a viral illness. Reye's syndrome is a very rare disease which affects the brain and liver and can be fatal. For this reason, children and teenagers (under 16 years of age) who have or are recovering from chicken pox or flu-like symptoms should not use this product, unless prescribed by a physician. When using this product, if changes in behavior 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.

Concomitant use of aspirin with other systemic NSAID's including cyclooxygenase-2-seletive inhibitors, should be avoided due to the potential for additive undesirable effects.

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 aspirin therapy.

Elderly: The elderly have an increased frequency of adverse reactions to NSAIDs, including GRAND-PA, especially gastrointestinal bleeding and perforation (PUBs), which may be fatal.

The risk of gastrointestinal bleeding or perforation (PUBs) is higher with increasing doses of GRAND-PA, in patients with a history of ulcers, and the elderly.

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 GRAND-PA, treatment with GRAND-PA should be stopped.

GRAND-PA should be given with caution to patients with a history of gastrointestinal disease (e.g. ulcerative colitis, Crohn's disease, hiatus hernia, gastro-oesophageal reflux disease, angiodysplasia) as the condition may be exacerbated.

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported. GRAND-PA should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of

hypersensitivity.

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

Doses of more than 1 g aspirin daily may precipitate acute haemolytic anaemia in patients with G6PDH deficiency.

Regular use of NSAIDs such as GRAND-PA 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.

Paracetamol

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

Patients suffering from liver or kidney 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 may increase the risk of metabolic acidosis.

Caffeine

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

Effects on ability to drive and use machines:

GRAND-PA has no or negligible influence on the ability to drive or the use of machinery.

INTERACTIONS:

Aspirin, paracetamol and caffeine combination medicines should not be used together with other non-steroidal anti-inflammatory medicines (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 Non-Steroidal Anti-Inflammatory Drugs (NSAIDs): Use of two or more NSAIDs concomitantly could result in an increase in side effects.

Corticosteroids: increased risk of gastrointestinal ulceration or bleeding (PUBs).

Anticoagulants and Platelet Aggregation Inhibitors: GRAND-PA 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 aspirin 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 contained in GRAND-PA, 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 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, it is necessary to ensure adequate hydration of the patient to monitor the kidney function and blood pressure, particurly when starting diuretic treatment.

Phenytoin: Aspirin increases serum levels of phenytoin; serum phenytoin should be well monitored.

Valproate: Aspirin inhibits its metabolism and hence could increase its toxicity; valproate levels should be well monitored.

Methotrexate (≤15 mg/ week): The toxicity of methotrexate may be enhanced by concomitant use of aspirin. In case of concomitant use with aspirin, renal function should be monitored.

Sulphonylureas: Aspirin, as contained in GRAND-PA, may enhance the activity oral antidiabetic preparations 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.

Alcohol: Co-administration of alcohol and aspirin increases the risk of gastrointestinal

haemorrhage.

Diuretics and antihypertensive agents: Concomitant use of aspirin with diuretics or antihypertensive agents (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 drugs may be associated with increased serum potassium levels, which should therefore be monitored frequently.

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

Selective serotonin reuptake inhibitors (SSRIs): Concurrent use of aspirin and SSRI's can increased the risk of gastrointestinal bleeding.

Barbiturates and other sedatives may mask the respiratory symptoms of aspirin overdosage and have been reported to enhance its toxicity.

Paracetamol

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

Caffeine

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

HUMAN REPRODUCTION:

Pregnancy

The safety of this preparation in pregnancy and lactation has not been established. GRAND PA is not recommended for use during pregnancy and is contraindicated during the third trimester of pregnancy (See Contraindications). Pregnant women should seek medical advice before taking GRAND PA

Aspirin 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 GRAND-PA 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, 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.

Lactation

Not recommended for use during breastfeeding.

Aspirin is secreted into breastmilk in low concentrations. There is insufficient information on the effects of aspirin at low concentration in infants. Treatment should be avoided during lactation because of the possible risk of Reye's syndrome and the potential impairment of platelet function in the infant. Paracetamol is excreted in breastmilk but not in a significant amount at

recommended dosages. Caffeine in breastmilk may potentially have a stimulating effect on breast fed infants but significant toxicity has not been observed.

DOSAGE AND DIRECTIONS FOR USE:

Do not exceed the stated dose.

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

TABLETS: ADULTS: Two tablets to be taken with water every three hours.

Maximum daily dose: 12 tablets

Minimum dosing interval: 3 hours

POWDERS: 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.

Should not be taken with other aspirin or paracetamol containing products.

Maximum daily dose: 6 powder wrappers/ sachets

Minimum dosing interval: 3 hours

SIDE EFFECTS:

Adverse reactions are tabulated below by System Organ Class (SOC) and frequency. The following convention has been utilized for the classification of undesirable effects: very common (≥1/10), common (≥ 1/100, <1/10), uncommon (≥1/1000, <1/100), rare (≥1/10 000, <1/1000), very rare (<1/10 000), not known (cannot be estimated from available data).

Adverse reactions identified during post-marketing use are reported voluntarily from a population of uncertain size, the frequency of these reactions is not known but likely to be rare or very rare (<1/1000).

Aspirin:

Body System	Undesirable Effect	Frequency
Blood and Lymphatic System Disorders	Prolonged bleeding time, thrombocytopenia, ecchymosis	Unknown
Cardiovascular Disorders	Oedema, hypertension, cardiac failure.	Unknown
Immune System Disorders	Hypersensitivity reactions (e.g. anaphylaxis, angioedema, paroxysmal bronchospasm, dyspnea, urticaria, skin reactions and rhinitis)	Unknown
Metabolism and Nutrition Disorders	Sodium and Fluid retention	Unknown
Ear and Labyrinth Disorders	Temporary hearing loss, tinnitus	Unknown
Gastrointestinal Disorders	Peptic ulcers, perforation or gastrointestinal bleeding, sometimes fatal. Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease, gastritis.	Unknown
Hepatobiliary Disorders	Reye's Syndrome (see Warnings and Precautions), Elevation in transaminase levels.	Unknown
Renal and Urinary Disorders	Renal dysfunction, increased blood uric acid levels	Unknown

Skin and subcutaneous tissue disorders:	Bullous reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis.	Unknown
Other	Dizziness	Unknown

Paracetamol:

Body System	**Undesirable Effect**	**Frequency**
Blood and Lymphatic System	Thrombocytopenia, leucopenia, pancytopenia, neutropenia and agranulocytosis.	Very rare
Immune System Disorders	Anaphylaxis, cutaneous hypersensitivity reactions including among others, skin rashes (erythematous or urticarial, may be more serious and accompanied by fever and mucosal lesions), angioedema, Steven-Johnson syndrome and Toxic Epidermal necrolysis.	Very rare
Other	Pancreatitis	Unknown

Caffeine:

Body System	**Undesirable Effect**	**Frequency**
Central Nervous System	Dizziness, headache	Unknown

Cardiac Disorders	Palpitation	Unknown
Psychiatric Disorders	Insomnia, restlessness, anxiety and irritability, nervousness	Unknown
Gastrointestinal Disorders	Nausea, increased gastric secretions, may cause gastric ulceration. Gastrointestinal disturbances	Unknown

Adverse events are more likely to occur with increasing dose and duration of use.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

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 Centre (contact details: Phone: 0861-555-777; Website: http://www.paediatrics.uct.ac.za/poisons-information-centre; Email: poisonsinformation@uct.ac.za) 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:

These include dizziness, tinnitus, vertigo, deafness, sweating, nausea, vomiting, mental confusion, increased respiratory rate, hyperventilation, warm extremities with bounding pulses, respiratory alkalosis, metabolic acidosis, ketosis and depression of the central nervous system. In children serious signs of overdosage may develop rapidly.

Uncommon features include haematemesis, hyperpyrexia, hypogylcaemia, hypokalaemia,

thrombocytopaenia, increased INR/ PTR, intravascular coagulation, renal failure and non-cardiac pulmonary oedema. Central nervous system features including confusion, disorientation, coma and convulsions are less common in adults than in children.

Paracetamol:

Susceptibility to paracetamol toxicity is increased in patients who have taken repeated high doses (greater than 5 -10 g/day) of paracetamol for several days, in chronic alcoholism, chronic liver disease, AIDS, malnutrition, and with the use of drugs that induce liver microsomal oxidation such as barbiturates, isoniazid, rifampicin, phenytoin and carbamazepine.

Symptoms of paracetamol overdosage in the first 24 hours are pallor, nausea, vomiting, anorexia and abdominal pain. Symptoms during the first 2 days of acute poisoning do not reflect the potential seriousness of the overdosage. Liver damage may become apparent 12 to 48 hours, or later after ingestion, initially by elevation of serum transaminase and lactic dehydrogenase activity, increased serum bilirubin concentration and prolongation of prothrombin time. The liver damage may progress 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 arrhythmias have been reported. Nausea, vomiting, anorexia and abdominal pain may persist for a week or more. Cerebral oedema and nonspecific myocardial depression have also occurred.

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.

Although evidence is limited it is recommended that any adult person who has ingested 5 - 10 grams or more of paracetamol (or a child who has had more than 140 mg/kg) within the preceding four hours, should have the stomach emptied by lavage (emesis may be adequate for children) and 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). In patients who are stuperose or comatose endotracheal intubation should precede gastric lavage to avoid aspiration.

N-acetylcysteine:

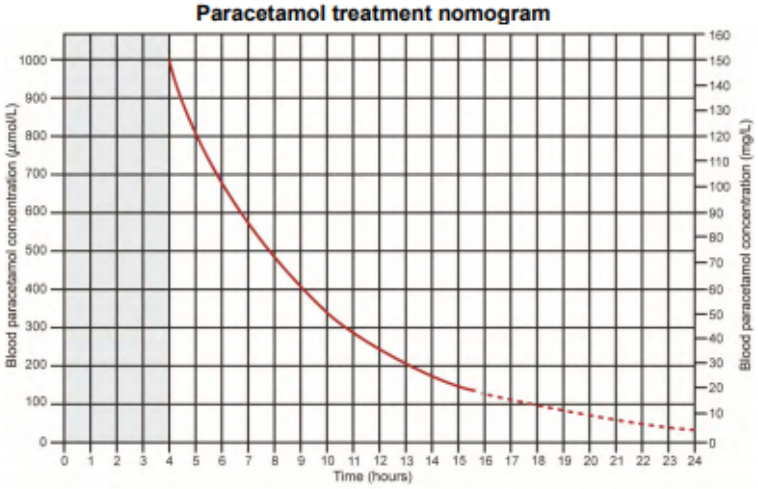
N-acetylcysteine should be administered to all cases of suspected overdose as soon as possible, preferably within 8 hours of overdosage, although treatment up to 36 hours after ingestion may still be of benefit, especially if more than 150 mg/kg of paracetamol was taken.

IV: An initial dose of 150 mg/kg in 200 ml glucose injection, given intravenously over 15 minutes, followed by an intravenous infusion of 50 mg/kg in 500 ml of glucose injection over the next 4 hours and then 100 mg/kg in 1 000 ml over the next 16 hours. The volume of intravenous fluids should be modified for children.

Orally: Oral formulation is not the treatment of choice, however 140 mg/kg may be administered as a 5 % solution initially, followed by a 70 mg/kg solution every 4 hour for 17

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.



Source: Daly FF, Fountain JS, Murray L, Graudins A, Buckley NA; Panel of Australian and New Zealand clinical toxicologists. Guidelines for the management of paracetamol poisoning in Australia and New Zealand -explanation and elaboration. A consensus statement from clinical toxicologists consulting to the Australasian poisons information centres. Med J Aust. 2008 Mar 3;188(5):296-301.

LoE:III[xiii]

Normogram extracted from Essential Medicines Guideline, South African Department of Health, 2015.

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 correlates best with survival. Monitor all patients with significant ingestions for at least ninety-

six hours.

Caffeine:

Large doses may cause epigastric pain, vomiting, diuresis, cardiac arrhythmia, restlessness, excitement, agitation, anxiety, convulsions, muscle tremor, tinnitus, scintillating scotoma, tachycardia and extrasystoles.

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.

The latest information regarding the treatment of overdosage can be obtained from the nearest Poison Centre.

IDENTIFICATION:

GRAND-PA HEADACHE TABLETS: Round bisected white tablet embossed with chevron.

GRAND-PA HEADACHE POWDERS: Fine, white powder.

PRESENTATION:

GRAND-PA HEADACHE TABLETS: In child resistant packs of, 24, 50 and 76 tablets, and in packs of 2, 10 and 38.

GRAND-PA HEADACHE POWDERS: Wrappers of 848 mg in packs of 10, 12, 20, 25 and 38 and sachets of 848 mg in single doses.

STORAGE INSTRUCTIONS:

Store in a cool dry place, at or below 25 ºC.

KEEP OUT OF THE REACH OF CHILDREN

REGISTRATION NUMBERS:

GRAND-PA HEADACHE TABLETS: P/2.9/22

GRAND-PA HEADACHE POWDERS: B/2.9/1113

NAME AND BUSINESS ADDRESS OF THE REGISTRATION HOLDER:

GlaxoSmithKline Consumer Healthcare South Africa (Pty) Ltd

39 Hawkins Avenue

Epping Industria 1

7460

DATE OF PUBLICATION OF THIS PACKAGE INSERT:

The date of registration of the medicine (GRAND-PA HEADCAHE POWDERS): 26 April 1983

The date of registration of the medicine (GRAND-PA HEADACHE TABLETS): 10 August 1981

Date of the most recent amendment to the professional information as approved by the Authority: 30 April 2019.

SCHEDULING STATUS AND REGISTRATION NUMBERS ALLOCATED BY OTHER NATIONAL MEDICINES REGULATORS:

GRAND-PA HEADACHE POWDERS:	**GRAND-PA HEADACHE TABLETS:**
NS0 Namibia Reg No 11/2.9/0186	NS0 Namibia Reg No 11/2.9/0187
S4 Botswana Reg No BOT1803248	S4 Botswana Reg No B9304615
GSL Malawi Reg No PMPB/PL260/23	Mozambique Reg No 2592
Mozambique Reg No 2793	GS Zambia Reg No 025/017

GS Zambia Reg No 025/019	HR Zimbabwe Reg No 2013/2.2/4787
HR Zimbabwe Reg No 74/2.2/0440	