Professional information for VARIPAN SUGAR FREE SYRUP

SCHEDULING STATUS: S0

1. NAME OF THE MEDICINE

VARIPAN SUGAR FREE SYRUP, 120 mg/5 mL

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 mL contains 120 mg paracetamol.

Excipients with known effects:

Contains 0,2 % *m/v* methylhydroxybenzoate and 0,02 % *m/v* propylhydroxybenzoate as preservatives.

Contains sweetener (18,5 mg sodium saccharin per 5 mL).

Sugar free.

Tartrazine free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Syrup.

Clear, sweet, chocolate mint flavoured, green syrup.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

VARIPAN SUGAR FREE SYRUP is indicated for the symptomatic treatment of mild to moderate pain and fever.

4.2 Posology and method of administration

Posology

DO NOT EXCEED THE RECOMMENDED DOSE.

Infants:

Under 3 months: 10 mg/kg (0,41 mL/kg)

3 months to 1 year: 2,5 – 5 mL (60 – 120 mg)

Children:

1 to 5 years: 5 – 10 mL (120 – 240 mg)

6 to 12 years: 10 – 20 mL (240 – 480 mg)

While symptoms persist, to be repeated every 4 hours if needed to a maximum of 4 doses per 24 hours for no longer than 5 days.

Method of administration

Oral administration.

4.3 Contraindications

- Hypersensitivity to paracetamol or to any of the excipients of VARIPAN SUGAR FREE SYRUP listed in section 6.1.
- Severe liver function impairment.

4.4 Special warnings and precautions for use

VARIPAN SUGAR FREE SYRUP contains paracetamol which may be fatal in overdose. In the event of overdosage or suspected overdose and notwithstanding the fact that the person may be asymptomatic, the nearest doctor, hospital or poison centre must be contacted immediately.

Dosages of VARIPAN SUGAR FREE SYRUP in excess of those recommended may cause severe

liver damage.

Consult a medical practitioner if pain or fever persists or gets worse, if other symptoms occur or if redness and swelling is present, as these could be signs of a more serious condition.

Do not use product continuously without consulting a medical practitioner:

- **For pain** – for more than 5 days.
- **For fever** – for more than 3 days.

Patients suffering from hepatitis or alcoholism, or recovering from any form of liver disease, should not take excessive quantities of VARIPAN SUGAR FREE SYRUP.

Patients suffering from liver or kidney disease should take VARIPAN SUGAR FREE SYRUP under medical supervision.

VARIPAN SUGAR FREE SYRUP should be use with caution in renal disease, alcohol dependence, chronic malnutrition or dehydration.

High Anion gap metabolic acidosis (HAGMA)

Caution is advised if VARIPAN SUGAR FREE SYRUP is administered concomitantly with flucloxacillin due to increased risk of high anion gap metabolic acidosis (HAGMA), particularly in patients with severe renal impairment, sepsis, malnutrition and other sources of glutathione deficiency (e.g. chronic alcoholism), as well as those using maximum daily doses of VARIPAN SUGAR FREE SYRUP. Close monitoring, including measurement of urinary 5-oxoproline, is recommended.

Severe cutaneous adverse reactions (SCARs)

Severe cutaneous adverse reactions (SCARs) such as toxic epidermal necrolysis (TEN), Steven-Johnson syndrome (SJS), acute generalised exanthematous pustulosis (AGEP), drug rash with

eosinophilia and systemic symptoms (DRESS) or drug-induced hypersensitivity syndrome (DIHS) and fixed drug eruptions (FDE) have been reported in patients treated with paracetamol containing medicines. If a patient develops SCARs, treatment with VARIPAN SUGAR FREE SYRUP must immediately be discontinued and appropriate treatment instituted.

VARIPAN SUGAR FREE SYRUP contains methylhydroxybenzoate and propylhydroxybenzoate: These may cause allergic reactions (possibly delayed).
VARIPAN SUGAR FREE SYRUP contains less than 1 mmoL sodium (23 mg) per 5 mL, that is to say essentially sodium-free.

4.5 Interaction with other medicines and other forms of interaction

Hepatotoxic medicines

Increased risk of hepatotoxicity.

Enzyme-inducing medicines

Increased risk of hepatotoxicity. Possible decrease in therapeutic effects of VARIPAN SUGAR FREE SYRUP.

Metoclopramide

Absorption of VARIPAN SUGAR FREE SYRUP may be accelerated.

Colestyramine

Absorption of VARIPAN SUGAR FREE SYRUP is reduced if given within one hour of colestyramine.

Salicylates

Prolonged concurrent use of VARIPAN SUGAR FREE SYRUP with salicylates increases the risk of adverse renal effects.

Warfarin and anticoagulant medicines

Concurrent, chronic, high-dose administration of VARIPAN SUGAR FREE SYRUP may increase the anticoagulant effect. Paracetamol as in VARIPAN SUGAR FREE SYRUP, is recommended as the general analgesic and antipyretic of choice in patients on oral anticoagulant therapy. However, caution is needed since, although it has no effect on the gastric mucosa or on platelet function, some studies (with warfarin, anisindione, dicoumarol, or phenprocoumon) and isolated reports have found an increased risk of bleeding in patients taking regular doses of paracetamol while on an oral anticoagulant. An increase in international normalised ratio (INR) has also been reported in controlled studies of the use of paracetamol in patients stabilised on warfarin. Increased monitoring of anticoagulant therapy may be appropriate for those also taking paracetamol, as in VARIPAN SUGAR FREE SYRUP, regularly.

Antiepileptic medicines

The plasma-paracetamol concentrations considered an indication for antidote treatment should be halved in patients receiving enzyme inducing medicines such as carbamazepine, phenobarbital, phenytoin, or primidone.

Probenecid

Pre-treatment with probenecid can decrease paracetamol, as in VARIPAN SUGAR FREE SYRUP, clearance and increase its plasma half-life. Although urinary excretion of the sulphate and glucuronide conjugates of paracetamol are reduced, that of paracetamol is unchanged.

Antibacterial medicines

The plasma-paracetamol concentrations considered an indication for antidote treatment should be halved in patients receiving enzyme inducing medicines such as rifampicin. Severe hepatotoxicity at therapeutic doses or moderate overdoses of paracetamol has been reported in patients receiving isoniazid, alone or with other medicines for tuberculosis.

Antiviral medicines

Severe hepatotoxicity has occurred after use of paracetamol, as in VARIPAN SUGAR FREE SYRUP, in a patient taking zidovudine and co-trimoxazole. However, neither short-term nor long-term studies (the latter also in an individual patient) have shown any alteration of zidovudine elimination in patients taking zidovudine and paracetamol, as in VARIPAN SUGAR FREE SYRUP.

Interferon alfa

Paracetamol, as in VARIPAN SUGAR FREE SYRUP, has also been found to enhance the antiviral effect of interferon alfa.

Flucloxacillin

Caution should be taken when VARIPAN SUGAR FREE SYRUP is used concomitantly with flucloxacillin as concurrent intake has been associated with high anion gap metabolic acidosis, especially in patients with risks factors (see section 4.4).

4.6 Fertility, pregnancy and lactation

Safety and efficacy in pregnancy and lactation has not been established. No data available on fertility.

4.7 Effects on ability to drive and use machines

VARIPAN SUGAR FREE SYRUP has no or negligible influence on the ability to drive a vehicle or use machines.

4.8 Undesirable effects

Blood and lymphatic system disorders

Less frequent: Agranulocytosis, thrombocytopenia, leucopenia, pancytopenia, neutropenia, anaemia.

Immune system disorders

Less frequent: Anaphylactic reaction, hypersensitivity reactions characterised by urticaria, dyspnoea and hypotension.

Metabolism and nutrition disorders

Frequency unknown: Pyroglutamic aciduria (5-oxoprolinuria) and high-anion gap metabolic acidosis.

Ear and labyrinth disorders

Frequency unknown: Hearing loss.

Cardiac disorders

Frequency unknown: Possible increase in the risk of hypertension.

Gastrointestinal disorders

Less frequent: Pancreatitis.

Frequency unknown: Nausea and vomiting.

Hepato-biliary disorders

Less frequent: Hepatitis.

Skin and subcutaneous tissue disorders

Less frequent: Dermatitis, skin rash and other allergic reactions such as toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), acute generalised exanthematous pustulosis (AGEP), drug rash with eosinophilia and systemic symptoms (DRESS) or drug-induced hypersensitivity syndrome (DIHS) and fixed drug eruptions (FDE) (see section 4.4). The rash is usually

erythematous or urticarial but sometimes more serious and accompanied by fever and mucosal lesion. More mild rashes and other hypersensitivity reactions also occur occasionally.

Renal and urinary disorders

Less frequent: Renal colic, renal failure and sterile pyuria.

Frequency unknown: Nephropathy.

Investigations

Frequency unknown: Increased transaminases. Low level transaminase elevations may occur in some patients taking therapeutic doses of paracetamol, as in VARIPAN SUGAR FREE SYRUP. These elevations are not accompanied with liver failure and usually resolve with continued therapy or discontinuation of paracetamol, as in VARIPAN SUGAR FREE SYRUP.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of VARIPAN SUGAR FREE SYRUP is important. It allows continued monitoring of the benefit/risk balance of VARIPAN SUGAR FREE SYRUP. Health care providers are asked to report any suspected adverse reactions to the South African Health Products Regulatory Authority (SAHPRA) via the 6.04 Adverse Drug Reaction Reporting Form, found online under SAHPRA's publications:

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

4.9 Overdose

Prompt treatment is essential. In the event of an overdose, consult a doctor immediately, or take the person directly to a 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 – 10 g/day) of paracetamol for several days, in chronic alcoholism, chronic liver disease, AIDS, malnutrition, and with the use of medicines that induce liver microsomes, such as barbiturates, isoniazid, rifampicin, phenytoin and carbamazepine.

Symptoms of overdose

Symptoms of paracetamol overdose in the first 24 hours include pallor, nausea, vomiting, anorexia and possibly abdominal pain. Mild symptoms during the first two days of acute poisoning do not affect the potential seriousness of the overdose.

Liver damage may become apparent 12 to 48 hours, or later after ingestion, initially by elevation of the serum transaminase and lactic dehydrogenase activity, increased serum bilirubin concentration and prolongation of the prothrombin time. 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 arrhythmias have been reported.

Treatment of overdose

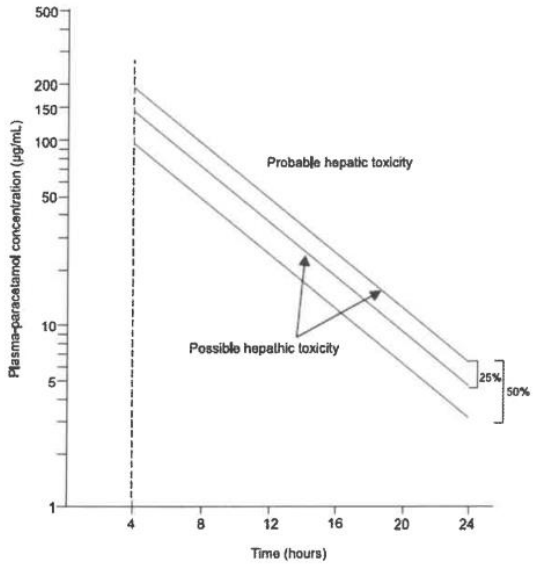
Although evidence is limited, it is recommended that any adult who has ingested 5 – 10 g or more of paracetamol (or child who has had more than 140 mg/kg) within the preceding four hours, should have the stomach emptied by lavage (emesis may be adequate for children) and a single dose of 50 g activated 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 stuporous or comatose, endotracheal intubations should precede gastric lavage in order to avoid aspiration.

***N*-acetylcysteine** should be administrated 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. An initial dose of 150 mg/kg *N*-acetylcysteine in 200 mL dextrose injection given **intravenously** over 15 minutes, followed by an infusion of 50 mg/kg in 500 mL dextrose injection over the next four hours, and then 100 mg/kg in 1 000 mL dextrose injection over the next sixteen hours. **The volume of the intravenous fluid should be modified for children.**

Although the oral formulation is not the treatment of choice, 140 mg/kg dissolved in water may be administrated initially, followed by 70 mg/kg every four hours for seventeen doses.
A plasma paracetamol level should be determined four hours after ingestion in all cases of suspected overdosage. Levels done before four hours, unless high, 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.

Paracetamol nomogram: A semi-logarithmic plot of plasma-paracetamol concentration against hours after 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 correlates best with survival.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A.2.7 Antipyretics or antipyretic and anti-inflammatory analgesics

Pharmacotherapeutic groups: Other Analgesics and Antipyretics (Anilides)

ATC code: N02BE01

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

5.2 Pharmacokinetic properties

Absorption

Following oral administration, paracetamol is well absorbed, with peak plasma concentrations obtained after 0,5 to 1 hour. The plasma half-life is about 2 hours.

Distribution

Plasma protein binding is variable.

Paracetamol is distributed into most body tissues. It crosses the placenta and is present in breast milk.

Elimination

Paracetamol is metabolised in the liver primarily by conjugation with glucuronic acid (about 60 %), sulphuric acid (about 35 %) and cysteine (about 3 %). Paracetamol is renally excreted primarily as conjugated metabolites.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Brilliant Blue H7250 (CI 42090)

Chocolate flavour R102

Citric acid monohydrate (E330)

Glycerine (E422)

Hypromellose (Methocel E4M) (E464)

Methylhydroxybenzoate (E218)

Peppermint essence

Propylene glycol (E1520)

Propylhydroxybenzoate (E216)

Purified water

Sodium citrate (E331)

Sodium saccharin (E954)

Quinoline Yellow (CI 47005).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

Store at or below 25 °C.

6.4 Special precautions for storage

Store in well-closed containers, protected from light.

6.5 Nature and contents of container

Medical round amber glass bottle of 100 mL with a 28 mm white cap or white HDPE bottle of 100 mL with a 31,5 mm white cap.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

LeBasi Pharmaceuticals (Pty) Ltd

San Domenico Building, Unit 6, Ground Floor

10 Church Street

Durbanville 7551

8. REGISTRATION NUMBER

38/2.7/0201

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 17 April 2009

10. DATE OF REVISION OF THE TEXT

20 November 2023