SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Pantoprazole Kalceks 40 mg lyophilised powder for solution for injection or infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 40 mg pantoprazole (as sodium sesquihydrate).

For the full list of excipients, see section *List of excipients*.

3. PHARMACEUTICAL FORM

Powder for solution for injection or infusion (lyophilised powder).
White or almost white uniform porous cake.
Description after reconstitution: clear, yellowish solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Short term use for symptomatic improvement and healing of gastrointestinal diseases which require a reduction in acid secretion:

- Duodenal ulcer
- Gastric ulcer
- Moderate and severe reflux oesophagitis
- Zollinger-Ellison syndrome and other pathological hypersecretory conditions

4.2 Posology and method of administration

The intravenous administration of pantoprazole is recommended only if oral application is not appropriate. The recommended dose for gastric and duodenal ulcer and moderate and severe reflux esophagitis is one vial of 40 mg pantoprazole per day. For the long-term management of Zollinger-Ellison syndrome and other pathological hypersecretory conditions the recommended daily dose at the beginning of the treatment is 80 mg pantoprazole. Thereafter, the dosage can be titrated up or down as needed using measurements of gastric acid secretion to guide. With doses above 80 mg daily, the dose should be divided and given twice daily. A temporary increase of the dosage above 160 mg pantoprazole is possible but should not be applied longer than required for adequate acid control. In case a rapid acid control is required, a starting dose of 2 x 80 mg pantoprazole is sufficient to manage a decrease of acid output into the target range (<10 mEq/h) within one hour in the majority of patients. Transition from pantoprazole to the oral formulation of pantoprazole should be performed as soon as it is clinically justified.

<u>Special populations</u>

Impaired hepatic function
A daily dose of 20 mg pantoprazole (half a vial of 40 mg pantoprazole) should not be exceeded in patients with severe liver impairment (see section *Special warnings and precautions for use*).

Impaired renal function
No dose adjustment is necessary in patients with impaired renal function.

Type and duration of treatment
As soon as oral therapy is possible, parenteral treatment with pantoprazole should be discontinued and 40 mg pantoprazole p.o. should be administered instead.

Method of administration

Intravenous use.

This medicinal product should be reconstituted, or reconstituted and diluted, before use. It should be administered intravenously over 2-15 minutes.

4.3 Contraindications

Pantoprazole Kalceks should not be used in cases of known hypersensitivity to its constituents.

4.4 Special warnings and precautions for use

Bone fracture
Proton pump inhibitors, especially if used in high doses and over long durations (> 1 year), may modestly increase the risk of hip, wrist and spine fracture, predominantly in the elderly or in presence of other recognised risk factors. Observational studies suggest that proton pump inhibitors may increase the overall risk of fracture by 10–40%. Some of this increase may be due to other risk factors. Patients at risk of osteoporosis should receive care according to current clinical guidelines and they should have an adequate intake of vitamin D and calcium.

Clostridium difficile diarrhea
Published observational studies suggest that PPI therapy may be associated with an increased risk of *Clostridium difficile* associated diarrhea, especially in hospitalized patients. This diagnosis should be considered for diarrhea that does not improve. Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

Hypomagnesaemia
Severe hypomagnesaemia has been reported in patients treated with PPI like Pantoprazole Kalceks for at least three months, and in most cases for a year. Serious manifestations of hypomagnesaemia such as fatigue, tetany, delirium, convulsions, dizziness and ventricular arrhythmia can occur but they may begin insidiously and be overlooked. In most affected patients, hypomagnesaemia improved after magnesium replacement and discontinuation of the PPI.
For patients expected to be on prolonged treatment or who take PPI with digoxin or drugs that may cause hypomagnesaemia (e.g., diuretics), health care professionals should consider measuring magnesium levels before starting PPI treatment and periodically during treatment.

Vitamin B12 deficiency
Daily treatment with any acid-suppressing medications over a long period of time (e.g., longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B12) caused by hypo- or achlorhydria. Rare reports of cyanocobalamin deficiency occurring with acid-suppressing therapy have been reported in the literature. This diagnosis should be considered if clinical symptoms consistent with cyanocobalamin deficiency are observed.

Interference with laboratory tests
Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours. If the patient(s) are due to have a test on Chromogranin A level, Pantoprazole Kalceks treatment should be stopped for at least 5 days before CgA measurements to avoid this interference (see section Pharmacodynamic properties). If CgA and gastrin levels have not returned to reference range after initial measurement, measurements should be repeated 14 days after cessation of proton pump inhibitor treatment.

Severe cutaneous adverse reactions
Severe cutaneous adverse reactions, including erythema multiforme, Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP) have been reported in association with the use of PPIs (see Undesirable Effects). Discontinue pantoprazole at the first signs or symptoms of severe cutaneous adverse reactions or other signs of hypersensitivity and consider further evaluation.

Hepatic impairment
In patients with severe liver impairment the liver enzymes should be monitored regularly during treatment with pantoprazole, particularly on long-term use. In the case of a rise of the liver enzymes the treatment should be discontinued.

HIV protease inhibitors
Co-administration of pantoprazole is not recommended with HIV protease inhibitors for which absorption is dependent on acidic intragastric pH such as atazanavir, nelfinavir; due to significant reduction in their bioavailability.

Methotrexate
Concomitant use with high dose methotrexate may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities.

Gastric malignancy
Symptomatic response to pantoprazole does not preclude the presence of gastric malignancy.

Regular surveillance
Patients on proton pump inhibitor treatment (particularly those treated for long term) should be kept under regular surveillance.

Subacute cutaneous lupus erythematosus (SCLE)
Proton pump inhibitors are associated with very infrequent cases of subacute cutaneous lupus erythematosus (SCLE). If lesions occur, especially in sun-exposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and the health care professional should consider stopping Pantoprazole Kalceks. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors.

4.5 Interaction with other medicinal products and other forms of interaction

Drugs with pH-dependent absorption pharmacokinetics
Pantoprazole may interfere with the absorption of drugs where gastric pH is an important determinant of oral bioavailability.

HIV protease inhibitors
Co-administration of pantoprazole is not recommended with HIV protease inhibitors for which absorption is dependent on acidic intragastric pH such as atazanavir, nelfinavir; due to significant reduction in their bioavailability.

Methotrexate
Concomitant use with high dose methotrexate may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities.

Other interaction studies
Pantoprazole is extensively metabolized in the liver via the cytochrome P450 enzyme system. The main metabolic pathway is demethylation by CYP2C19 and other metabolic pathways which include oxidation by CYP3A4. Interaction studies with drugs also metabolized with these pathways, including carbamazepine, diazepam, glibenclamide, nifedipine, phenytoin, and an oral contraceptive containing levonorgestrel and ethinyl oestradiol did not reveal clinically significant interactions.
An interaction of pantoprazole with other drugs or compounds, which are metabolized using the same enzyme system, cannot be excluded.
Results from a range of interaction studies demonstrate that pantoprazole does not affect the metabolism of active substances metabolized by CYP1A2 (such as caffeine, theophylline), CYP2C9 (such as piroxicam, diclofenac, naproxen), CYP2D6 (such as metoprolol), or CYP2E1 (such as ethanol) or does not interfere with p-glycoprotein related absorption of digoxin.
There were no interactions with concomitantly administered antacids.
Interaction studies have also been performed administering pantoprazole concomitantly with the respective antibiotics (clarithromycin, metronidazole, amoxicillin). No clinically relevant interactions were found.

Clopidogrel
Concomitant administration of pantoprazole and clopidogrel in healthy subjects had no clinically important effect on exposure to the active metabolite of clopidogrel or clopidogrel-induced platelet inhibition. No dose adjustment of clopidogrel is necessary when administered with an approved dose of pantoprazole.

Drugs that inhibit or induce CYP2C19 (tacrolimus, fluvoxamine)
Concomitant administration of pantoprazole and tacrolimus may increase whole blood levels of tacrolimus, especially in transplant patients who are intermediate or poor metabolizers of CYP2C19. Inhibitors of CYP2C19, such as fluvoxamine, would likely increase the systemic exposure of pantoprazole.

Coumarin anticoagulants (phenprocoumon or warfarin)
Co-administration of pantoprazole with warfarin or phenprocoumon did not affect the pharmacokinetics of warfarin, phenoprocoumon or INR. However, there have been reports of increased INR and prothrombin time in patients receiving PPIs and warfarin or phenoprocoumon concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding, and even death. Patients treated with pantoprazole and warfarin or phenprocoumon may need to be monitored for increase in INR and prothrombin time.

4.6 Pregnancy and lactation

The limited data on the use of pantoprazole in pregnant women does not indicate foetal/ neonatal toxicity. The potential risk for humans is unknown. Pantoprazole should not be used during pregnancy unless clearly necessary.
Animal studies have shown excretion of pantoprazole in breast milk. Excretion into human milk has been reported. Therefore a decision on whether to continue/discontinue breastfeeding or to continue/discontinue therapy with pantoprazole should be made taking into account the benefit of breastfeeding to the child and the benefit of pantoprazole therapy to women.

4.7 Effects on ability to drive and use machines

Pantoprazole is not expected to adversely affect the ability to drive or use machines. Adverse drug reactions such as dizziness and visual disturbances may occur. If affected, patients should not drive or operate machines.

4.8 Undesirable effects

The table below lists adverse reactions reported with pantoprazole, ranked under the following frequency classification:
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); not known (cannot be estimated from the available data).

For all adverse reactions reported from post-marketing experience, it is not possible to apply any Adverse Reaction frequency and therefore they are mentioned with a "not known" frequency.

Table 1. Adverse reactions with pantoprazole in clinical trials and post-marketing experience

Frequency / **System organ class**	**Common**	**Uncommon**	**Rare**	**Very rare**	**Not known**
Blood and lymphatic system disorders			Agranulocytosis	Thrombocytopenia; Leukopenia; Pancytopenia	
Eye disorders			Disturbances in vision / blurred vision		
Gastrointestinal disorders	Fundic gland polyps (benign)	Diarrhoea; Nausea / Vomiting; Abdominal distension and bloating; Constipation; Dry mouth; Abdominal pain and discomfort			Microscopic colitis
General disorders and administration site conditions	Injection site thrombophlebitis	Asthenia, fatigue and malaise	Body temperature increased; Oedema peripheral		
Hepatobiliary disorders		Liver enzymes increased	Bilirubin increased		Hepatocellular injury; Jaundice; Hepatocellular failure
Immune system disorders			Hypersensitivity (including anaphylactic reactions and anaphylactic shock)		
Infections and infestations					*Clostridium difficile* associated diarrhoea

Frequency / System organ class	Common	Uncommon	Rare	Very rare	Not known
Metabolism and nutrition disorders			Hyperlipidaemias; Weight changes		Hyponatraemia; Hypomagnesaemia ; Vitamin B12 deficiency; Hypocalcaemia*; Hypokalaemia*
Musculoskeletal and connective tissue disorders		Fracture of the hip, wrist or spine	Arthralgia; Myalgia		
Nervous system disorders		Headache; Dizziness	Taste disorders		
Psychiatric disorders		Sleep disorders	Depression	Disorientation	Hallucination; Confusion
Renal and urinary disorders					Tubulointerstitial nephritis (TIN) (with possible progression to renal failure); Interstitial nephritis
Reproductive system and breast disorders			Gynaecomastia		
Skin and subcutaneous tissue disorders		Rash/ exanthema/ eruption; Pruritus	Urticaria; Angioedema		Stevens-Johnson syndrome; Toxic epidermal necrolysis; Drug reaction with eosinophilia and systemic symptoms; Acute generalized exanthematous pustulosis; Erythema multiforme; Photosensitivity; Subacute cutaneous lupus erythematosus

* Hypocalcaemia and/or hypokalaemia may be related to the occurrence of hypomagnesaemia (see *Special warnings and precautions for use*)

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the National Centre for Adverse Drug Reaction Monitoring by visiting the website portal.npra.gov.my

4.9 Overdose

Systemic exposure with up to 240 mg administered intravenously over 2 minutes was well tolerated. As pantoprazole is extensively protein bound, it is not readily dialyzable.
In the case of overdose with clinical signs of intoxication, apart from symptomatic and supportive treatment, no specific therapeutic recommendations can be made.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Selective proton pump inhibitor, substituted benzimidazole
ATC code: A02BC02

Mechanism of action
Pantoprazole is a substituted benzimidazole which inhibits the secretion of hydrochloric acid in the stomach by specific blockade of the proton pumps of the parietal cells.

Pantoprazole is converted to its active form in the acidic environment in the parietal cells where it inhibits the H+, K+-ATPase enzyme, i.e. the final stage in the production of hydrochloric acid in the stomach. The inhibition is dose-dependent and affects both basal and stimulated acid secretion. In most patients, freedom from symptoms is achieved within 2 weeks. As with other proton pump inhibitors and H_2 receptor inhibitors, treatment with pantoprazole reduces acidity in the stomach and thereby increases gastrin in proportion to the reduction in acidity. The increase in gastrin is reversible. Since pantoprazole binds to the enzyme distal to the cell receptor level, it can inhibit hydrochloric acid secretion independently of stimulation by other substances (acetylcholine, histamine, gastrin). The effect is the same whether the product is given orally or intravenously.
The fasting gastrin values increase under pantoprazole. On short-term use, in most cases they do not exceed the upper limit of normal. During long-term treatment, gastrin levels double in most cases. An excessive increase, however, occurs only in isolated cases. As a result, a mild to moderate increase in the number of specific endocrine (ECL) cells in the stomach is observed in a minority of cases during long-term treatment (simple to adenomatoid hyperplasia). However, according to the studies conducted so far, the formation of carcinoid precursors (atypical hyperplasia) or gastric carcinoids as were found in animal experiments have not been observed in humans.

An influence of a long term treatment with pantoprazole exceeding one year cannot be completely ruled out on endocrine parameters of the thyroid according to results in animal studies.

Pharmacodynamic
During treatment with antisecretory medicinal products, serum gastrin increases in response to the decreased acid secretion. Also CgA increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours.
Available published evidence suggests that proton pump inhibitors should be discontinued between 5 days and 2 weeks prior to CgA measurements. This is to allow CgA levels that might be spuriously elevated following PPI treatment to return to reference range.

5.2 Pharmacokinetic properties

Absorption
After ingestion, pantoprazole is rapidly absorbed into the bloodstream. On average the maximum serum concentrations (C_{max}) of 1 to 1.5 µg/ml (pantoprazole 20 mg tablet) or 2 to 3 µg/ml (pantoprazole 40 mg tablet) are achieved at about 2 to 2.5 hours after administration. After single and repeated administration of pantoprazole, the pharmacokinetic characteristics of pantoprazole are very similar.

Both oral and IV administration of pantoprazole in the dose range of 10 mg to 80 mg result in linear serum pharmacokinetics. The absolute bioavailability from the tablet was found to be about 77%. Concomitant intake of food had no relevant influence either on the AUC or on the C_{max} and, thus, bioavailability. Only the variability of the lag-time will be increased by concomitant food intake.
With pantoprazole granules, the peak serum concentration of 1.9 mg/l is reached after 2-2.5 hours in the fasting state. The AUC is about 5.5 mgh/l. Concomitant food intake reduces both AUC and the peak serum concentration and delays the time to peak concentration. This effect is reduced by taking pantoprazole granules 30 minutes before breakfast.

Distribution
Pantoprazole's serum protein binding is about 98%, and in keeping with this, pantoprazole has a low volume of distribution (about 0.15 l/kg) and limited tissue distribution.

Metabolism
Pantoprazole is rapidly eliminated from the circulation and extensively metabolized in the liver. Metabolism occurs via oxidation by the CYP enzyme system, predominantly by CYP2C19 and CYP3A4 (Phase I metabolism, which is saturable). Pantoprazole undergoes further biotransformation by conjugation with sulphate, which involves the cytoplasmic enzyme sulphotransferase (phase II metabolism, which is not saturable), and which presents the main metabolism of pantoprazole.

Excretion and elimination
About 80% of the metabolites of pantoprazole are eliminated via the renal route, the rest via the faeces. None of the metabolites are considered as biologically active. The main metabolite in both the serum and urine is desmethylpantoprazole, which is conjugated with sulphate. T1/2 of the main metabolite is about 1.5 hour (which is not much longer than that of pantoprazole, 1 hour).

Special populations
Impaired renal function
In patients with impaired renal function (including dialysis), pantoprazole showed no prolonged elimination half-life and no accumulation when compared with healthy subjects. No dose adjustment is necessary in patients with impaired renal function.

Impaired hepatic function
In comparison with healthy subjects, after oral administration of pantoprazole sodium to patients with liver cirrhosis classified as Child-Pugh A and B, serum elimination half-lives of pantoprazole increased to between 3 and 6 hours (pantoprazole 20 mg tablet) or 7 to 9 hours (pantoprazole 40 mg tablet and powder) and AUC values increased by a factor of 3 to 5 (pantoprazole 20 mg tablet) or 5 to 7-fold (pantoprazole 40 mg tablet and powder). Maximum serum concentrations, C_{max}, in these patients increased only slightly (1.3-fold after oral administration, 1.5-fold after IV application) relative to healthy subjects. The observed pharmacokinetic changes did not lead to relevant accumulation following once-daily dosing.

Age, gender, race
As with other clinically used PPIs, a small percentage of the population (about 3% Caucasians, 20% Asians) shows slower elimination of pantoprazole (T1/2 being up to 10 hours as compared with 1 hour). Such persons are known as poor metabolizers as a result of a deficiency of the CYP2C19 enzyme. In these individuals the metabolism of pantoprazole is probably mainly catalysed by CYP3A4. After a single-dose administration of 40 mg pantoprazole, the mean area under the plasma concentration-time curve was approximately 6 times higher in poor metabolizers than in subjects having a functional CYP2C19 enzyme (extensive metabolizers). Mean peak plasma concentrations were increased by about 60%. These findings have no implications for the posology of pantoprazole.
Results from several studies in children/adolescents from birth to 16 years indicate that the pharmacokinetics of pantoprazole is similar to those in adults when appropriately adjusted by patient weight, despite somewhat decreased clearance in patients less than 1 year old. Similar to adults, pediatric patients who were poor metabolizers of CYP2C19, exhibited reduced clearance that was more than 70% lower than the typical value.

Compared with younger subjects, slight increases in AUC and C_{max} were noted after single and repeated oral administration of pantoprazole to healthy elderly subjects (age >65 years). However, no dose adjustment is necessary in elderly patients.

Drug interactions
Pantoprazole is metabolized in the liver via the CYP enzyme system. An interaction of pantoprazole with other drugs or compounds, which are metabolized using the same enzyme system, cannot be ruled out. Nevertheless, in specific tests pantoprazole did not affect the clearance of several compounds metabolized by CYP enzymes. Vice-versa, all drugs that were tested regarding their potential influence on the pharmacokinetics of pantoprazole had no relevant effect.
No detectable interactions between pantoprazole and any other commonly prescribed co-medication tested so far were found.
Metabolism of pantoprazole occurs via oxidation by the CYP enzyme system, predominantly by CYP2C19 and CYP3A4. Interaction studies with drugs also metabolized by these pathways, like carbamazepine, diazepam, glibenclamide, nifedipine, phenytoin, and an oral contraceptive containing levonorgestrel and ethinyl oestradiol did not reveal clinically significant interactions. Results from a range of interaction studies demonstrate that pantoprazole does not affect the metabolism of active substances metabolized by CYP1A2 (such as caffeine, theophylline), CYP2C9 (such as piroxicam, diclofenac, naproxen), CYP2D6 (such as metoprolol), or CYP2E1 (such as ethanol) and does not interfere with p-glycoprotein related absorption of digoxin. There were no interactions with concomitantly administered antacids. Interaction studies have also been performed administering pantoprazole concomitantly with the respective antibiotics (clarithromycin, metronidazole, amoxicillin). No clinically relevant interactions were found.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium citrate
Mannitol (E 421)
Sodium hydroxide (for pH adjustment)

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section *Special precautions for disposal and other handling*.

6.3 Shelf life

Unopened: 2 years

Shelf life after opening the vial
Once opened, the product should be used immediately.

Shelf life after reconstitution or reconstitution and dilution
The chemical and physical in-use stability after reconstitution, or reconstitution and dilution with sodium chloride 9 mg/ml (0.9%) solution for injection, has been demonstrated for 24 hours at 2 to 8 °C and 30 °C.
The chemical and physical in-use stability after reconstitution with sodium chloride 9 mg/ml (0.9%) solution for injection and dilution with glucose 50 mg/ml (5%) solution for injection has been demonstrated for 24 hours at 2 to 8 °C and for 12 hours at 30 °C.

From a microbiological point of view, the prepared solution should be used immediately. If not used immediately, in-use storage times and conditions prior to the use are the responsibility of the user and would not normally be longer than 24 hours at 2 to 8 °C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Do not store above 30 °C.
Keep the vials in the outer carton in order to protect from light.

6.5 Nature and contents of container

Pantoprazole Kalceks 40 mg lyophilised powder for solution for injection or infusion is produced in injection vials (ISO size 10R) made of Ph. Eur., Type I clear borosilicate tubular glass, with crimp neck. The 10 ml vials size are closed with 20 mm bromobutyl rubber stoppers and then over sealed with 20 mm aluminium crimp flip-off seals. The aluminium crimped flip-off seals consist out of two parts: an aluminium seal and a coloured polypropylene cover.
5 vials together with a paper package insert and placed into a paper outer carton.

6.6 Special precautions for disposal and other handling

For single use only.

A ready-to-use solution is prepared by injecting 10 ml of sodium chloride 9 mg/ml (0.9%) solution for injection into the vial containing the powder. The prepared solution may be administered directly or may be administered after mixing it with 100 ml sodium chloride 9 mg/ml (0.9%) solution for injection or glucose 50 mg/ml (5%) solution for injection.

The prepared solution should be visually inspected prior to use. The appearance of the product after reconstitution is a clear yellowish solution. Only clear solutions free from particles should be used.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. PRODUCT REGISTRATION HOLDER AND MANUFACTURER

Product Registration Holder:
Eucogen Sdn Bhd
6A, Jalan Sungai Burung U
32/U, Bukit Rimau, 40460 Shah
Alam, Selangor, Malaysia

Manufacturer:
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8. DATE OF REVISION OF THE TEXT

09/2025