Summary of Product Characteristics (SPC)

1. NAME OF THE MEDICINAL PRODUCT

Prokinin 5mg/ 5mL Suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml of suspension contains 5 mg of Domperidone.

3. PHARMACEUTICAL FORM

White to creamy homogeneous suspension with lemon flavor.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prokinin is used to relief symptoms of nausea and vomiting in adults and children.

4.2 Posology and method of administration

Oral Prokinin should be used at the lowest effective dose for the shortest duration necessary to control nausea and vomiting.

Patients should try to take each dose at the scheduled time. If a scheduled dose is missed, the missed dose should be omitted and the usual dosing schedule resumed. The dose should not be doubled to make up for a missed dose.

It is recommended to take oral domperidone before meals. If taken after meals, absorption of the drug is somewhat delayed.

See section 4.4. for further information,

Adults and adolescents (over 12 years and weighing 35 kg or more)

The recommended duration of treatment is 7 days (one week).

The recommended dose is 10 mg (10ml) up to three times daily with a maximum oral daily dose of 30 mg.

Infants and children (under 12 years of age and weighing less than 35kg)

0.25 mg/kg up to three times per day by mouth with a maximum daily dose of 0.75 mg/kg.

Hepatic Impairment

Domperidone is contraindicated in moderate or severe hepatic impairment (see section 4.3). Dose modification in mild hepatic impairment is however not needed (see section 5.2). Renal **Impairment**

Since the elimination half-life of domperidone is prolonged in severe renal impairment, on repeated administration, the dosing frequency of domperidone should be reduced to once or twice daily depending on the severity of the impairment, and the dose may need to be reduced. Such patients on prolonged therapy should be reviewed regularly (see sections 4.4 and 5.2)

4.3 Contraindications

Prokinin is contraindicated in the following situations:

- Known hypersensitivity to domperidone or any of the excipients - Prolactin-releasing pituitary tumour (prolactinoma).
- when stimulation of the gastric motility could be harmful,e.g .,in patients with gastrointestinal haemorrhage, mechanical obstruction or perforation.
- in patients with moderate or severe hepatic impairment (see section 5.2).
- Patients with certain heart conditions including heart failure, previous heart attack, angina (chest pains), and heart arrhythmia disorders.
- In patients who have known existing prolongation of cardiac conduction intervals, particularly QTc patients with significant electrolyte disturbances.
- Co-administration with QT-prolonging drugs.
- Co-administration with potent CYP3A4 inhibitors (regardless of their QT prolonging effects).

4.4 Special warnings and precautions for use

Cardiovascular effects

Domperidone has been associated with prolongation of the QT interval on the electrocardiogram. During post-marketing surveillance, there have been very rare cases of QT prolongation and torsades de pointes in patients taking domperidone. These reports included patients with confounding risk factors, electrolyte abnormalities and concomitant treatment which may have been contributing factors (see section 4.8).

Epidemiological studies showed that domperidone was associated with an increased risk of serious ventricular arrhythmias or sudden cardiac death (see section 4.8). A higher risk was observed in patients older than 60 years, patients taking daily doses greater than 30mg, and patients concurrently taking QT_prolonging drugs or CYP3A4 inhibitors.

Domperidone should be used at the lowest effective dose in adults and children.

Domperidone is contraindicated in patients with known existing prolongation of cardiac conduction intervals, particularly QTc, in patients with significant electrolyte disturbances (hypokalaemia, hyperkalaemia, hypomagnesaemia), or bradycardia, or in patients with underlying cardiac diseases such as congestive heart failure due to increased risk of ventricular arrhythmia (see section 4.3). Electrolyte disturbances (hypokalaemia, hyperkalaemia, hypomagnesaemia) or bradycardia are known to be conditions increasing the proarrythmic risk.

Treatment with domperidone should be stopped if signs or symptoms occur that may be associated with cardiac arrhythmia, and the patients should consult their physician.

Patients should be advised to promptly report any cardiac symptoms.

Co-administration of levodopa

Although no dosage adjustment of levodopa is deemed necessary, an increase of plasma levodopa concentration (max 30-40%) has been observed when domperidone was taken concomitantly with levodopa. See section 4.5.

Use in infants

Although neurological side effects are rare (see section 4.8), the risk of neurological side effects is higher in young children since metabolic functions and the blood-brain barrier are not fully developed in the first months of life. Overdosing may cause extrapyramidal symptoms in children, but other causes should be taken into consideration. Renal impairment

Since the elimination half-life of domperidone is prolonged in severe renal impairment, on repeated administration, the dosing frequency of domperidone should be reduced to once or twice daily depending on the severity of the impairment, and the dose may need to be reduced. Such patients on prolonged therapy should be reviewed regularly (see section 5.2).

Use with potent CYP3A4 inhibitors

Co-administration with oral ketoconazole, erythromycin or other potent CYP3A4 inhibitors that prolong the QTc interval should be avoided (see section 4.5). Excipients

The oral suspension contains sorbitol (E420). Patients with rare hereditary problems of fructose intolerance should not take this medicine**.** The oral suspension includes propylhydroxybenzoate (E216) and methylhydroxybenzoate **(**E218) which may cause allergic reactions (possibly delayed).

4.5 Interaction with other medicinal products and other forms of interaction

When antacids or antisecretory drugs are used concomitantly, they should not be taken simultaneously with oral formulations of domperidone.

Concomitant administration of anticholinergic drugs may antagonise the anti-dyspeptic effects of domperidone.

Increased risk of occurrence of QT-interval prolongation, due to pharmacodynamics and/or pharmacokinetic interactions.

Concomitant use of the following substances is contraindicated:

QTc-prolonging medicinal products

- Anti-arrhythmics class IA (e.g., disopyramide, hydroquinidine, quinidine)
- Anti-arrhythmics class III (e.g., amiodarone, dofetilide, dronedarone, ibutilide, sotalol)
- Certain antipsychotics (e.g., haloperidol, pimozide, setindole)
- Certain antidepressants (e.g., citalopram, escitalopram)
- Certain antibiotics (e.g., erythromycin, lefloxacin, moxifloxacin, spiramycin)
- Certain antifungal agents (e.g., pentamidine)
- Certain antmalarial agents (in particular halofantrine, lumefantrine)
- Certain gastro-intestinal medicines (e.g., cisapride, dolasetron, prucalopride)
- Certain antihistaminics (e.g., mequitazine, mizolastine)
- Certain medicines used in cancer (e.g., toremifene, vandetanib, vincamine)
- Certain other medicines (e.g., bepridil, diphemanil, methadone)

Potent CYP3A4 inhibitors (regardless of their QT prolonging effects), i.e.: -

Protease inhibitors

- Systemic azole antifungals
- Some macrolides (erythromycin, clarithromycin and telithromycin) (see section 4.3).

Concomitant use of the following substances is not recommended:

Moderate CYP3A4 inhibitors i.e. diltiazem, verapamil and some macrolides (see section 4.3).

Concomitant use of the following substances requires caution in use:

Caution with bradycardia and hypokalaemia-inducing drugs, as well as with the following macrolides involved in QT_interval prolongation: azithromycin and roxithromycin (clarithromycin is contraindicated as it is a potent CYP3A4 inhibitor).

Levodopa: Increase of plasma levels of levodopa (max 30-40%). See section 4.4 The above list of substances is representative and not exhaustive.

The main metabolic pathway of domperidone is through CYP3A4. In vitro data suggest that the concomitant use of drugs that significantly inhibit this enzyme may result in increased plasma levels of domperidone. Separate in vivo pharmacokinetic/pharmacodynamic interaction studies with oral ketoconazole or oral erythromycin in healthy subjects confirmed a marked inhibition of domperidone's CYP3A4 mediated first pass metabolism by these drugs.

With the combination of oral domperidone 10mg four times daily and ketoconazole 200mg twice daily, a mean QTc prolongation of 9.8 msec was seen over the observation period, with changes at individual time points ranging from 1.2 to 17.5 msec. With the combination of

domperidone 10mg four times daily and oral erythromycin 500mg three times daily, mean QTc over the observation period was prolonged by 9.9 msec, with changes at individual time points ranging from 1.6 to 14.3 msec. Both the Cmax and AUC of domperidone at steady state were increased approximately three-fold in each of these interaction studies.

In these studies domperidone monotherapy at 10mg given orally four times daily resulted in increases in mean QTc of 1.6 msec (ketoconazole study) and 2.5 msec (erythromycin study), while ketoconazole monotherapy (200mg twice daily) and erythromycin monotherapy (500mg three times daily) led to increases in QTc of 3.8 and 4.9 msec, respectively, over the observation period."

4.6 Pregnancy and lactation

Pregnancy

There are limited post-marketing data on the use of domperidone in pregnant women. Studies in animals have shown reproductive toxicity at maternally toxic doses (see section 5.3). Prokinin should only be used during pregnancy when justified by the anticipated therapeutic benefit.

Breast-feeding

Domperidone is excreted in human milk and breast-fed infants receive less than 0.1 % of the maternal weight-adjusted dose. Occurrence of adverse effects, in particular cardiac effects cannot be excluded after exposure via breast milk. A decision should be made whether to discontinue breast-feeding or to discontinue/abstain from domperidone therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.
Caution should be exercised in case of QTc prolongation risk factors in breast-fed infants."

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Tabulated list of adverse reactions

The safety of domperidone was evaluated in clinical trials and in postmarketing experience. The clinical trials included 1275 patients with dyspepsia, gastro-oesophageal reflux disorder (GORD), Irritable Bowel Syndrome (IBS), nausea and vomiting or other related conditions in 31 double-blind, placebo-controlled studies. All patients were at least 15 years old and received at least one dose of Prokinin (domperidone base). The median total daily dose was 30 mg (range 10 to 80 mg), and median duration of exposure was 28 days (range 1 to 28 days). Studies in diabetic gastroparesis or symptoms secondary to chemotherapy or parkinsonism were excluded.

The following terms and frequencies are applied:

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), Where frequency cannot be estimated from clinical trials data, it is recorded as "Not known".

System Organ Class	Adverse Drug Reaction Frequency		
	Common	**Uncommon**	**Not known**
Immune system disorders			Anaphylactic reaction (including anaphylactic shock)
Psychiatric disorders		Loss of libido Anxiety	Agitation Nervousness
Nervous system disorders		Somnolence Headache	Convulsion Extrapyramidal disorder Restless leg syndrome
Eye disorders			Oculogyric crisis
Cardiac disorders (see section 4.4)			Ventricular arrhythmias Sudden cardiac death QTc prolongation Torsades de Pointes
Gastrointestinal disorders	Dry mouth	Diarrhoea	
Skin and subcutaneous tissue disorder		Rash Pruritus	Urticaria Angioedema
Renal and urinary disorders			Urinary retention
Reproductive system and breast disorders		Galactorrhoea Breast pain	Gynaecomastia Amenorrhoea

		Breast tenderness	
General disorders and administration site conditions		Asthenia	
Investigations			Liver function test abnormal Blood prolactin increased

In 45 studies where domperidone was used at higher dosages, for longer duration and for additional indications including diabetic gastroparesis, the frequency of adverse events (apart from dry mouth) was considerably higher. This was particularly evident for pharmacologically predictable events related to increased prolactin. In addition to the reactions listed above, akathisia, breast discharge, breast enlargement, breast swelling, depression, hypersensitivity, lactation disorder, and irregular menstruation were also noted.

Paediatric population

Extrapyramidal disorder occurs primarily in neonates and infants.

Other central nervous system-related effects of convulsion and agitation also are primarily reported in infants and children.

4.9 Overdose

Symptoms

Overdose has been reported primarily in infants and children. Symptoms of overdosage may include agitation, altered consciousness, convulsions, disorientation, somnolence and extrapyramidal reactions. Treatment

There is no specific antidote to domperidone, but in the event of overdose, gastric lavage as well as the administration of activated charcoal, may be useful. Close medical supervision and supportive therapy is recommended.

Anticholinergic, anti-parkinson drugs may be helpful in controlling the extrapyramidal reactions.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Propulsives, ATC code: A03F A 03

Mechanism of action

Prokinin is a dopamine antagonist with anti-emetic properties, Prokinin does not readily cross the blood-brain barrier. In domperidone users, especially in adults, extrapyramidal side effects are very rare, but domperidone promotes the release of prolactin from the pituitary. Its antiemetic effect may be due to a combination of peripheral (gastrokinetic) effects and antagonism of dopamine receptors in the chemoreceptor trigger zone, which lies outside the blood-brain barrier in the area postrema. Animal studies, together with the low concentrations found in the brain, indicate a predominantly peripheral effect of domperidone on dopamine receptors.

Studies in man have shown oral domperidone to increase lower oesophaegeal pressure, improve antroduodenal motility and accelerate gastric emptying. There is no effect on gastricsecretion.

In accordance with ICH—E14 guidelines, a thorough QT study was performed. This study included a placebo, an active comparator and a positive control and was conducted in healthy subjects with up to 80 mg per day 10 or 20 mg administered 4 times a day of domperidone. This study found a maximal difference of QTc between domperidone and placebo in LSmeans in the change from baseline of 3.4 msec for 20 mg domperidone administered 4 times a day on Day 4. The 2-sided 90 % CI (1.0 to 5.9 msec) did not exceed 10 msec. No clinically relevant QTc effects were observed in this study when domperidone was administered at up to 80 mg/day (i.e., more than twice the maximum recommended dosing).

However, two previous drug-drug interaction studies showed some evidence of QTc prolongation when domperidone was administered as monotherapy (10 mg 4 times a day).The largest time-matched mean difference of QTcF between domperidone and placebo was 5.4 msec (95 % CI: -1.7 to 12.4) and 7.5 msec (95 % CI: 0.6 to 14.4), respectively.

5.2 Pharmacokinetic properties

Absorption

In fasting subjects, domperidone is rapidly absorbed after oral administration, with peak plasma concentrations at 30 to 60 minutes. The low absolute bioavailability of oral domperidone (approximately 15%) is due to an extensive first-pass metabolism in the gut wall and liver. Although domperidone's bioavailability is enhanced in normal subjects when taken after a meal, patients with gastro-intestinal complaints should take domperidone 15-30 minutes before a meal. Reduced gastric acidity impairs the absorption of domperidone. Oral bioavailability is decreased by prior concomitant administration of cimetidine and sodium bicarbonate. The time of peak absorption is slightly delayed and the AUC somewhat increased when the oral drug is taken after a meal.

Distribution

Oral domperidone does not appear to accumulate or induce its own metabolism; a peak plasma level after 90 minutes of 21 ng/ml after two weeks oral administration of 30 mg per day was almost the same as that of 18 ng/ml after the first dose. Domperidone is 91-93% bound to plasma proteins. Distribution studies with radiolabelled drug in animals have shown wide tissue distribution, but low brain concentration. Small amounts of drug cross the placenta in rats.

Biotransformation

Prokinin undergoes rapid and extensive hepatic metabolism by hydroxylation and Ndealkylation. *In vitro* metabolism experiments with diagnostic inhibitors revealed that CYP3A4 is a major form of cytochrome P-450 involved in the N-dealkylation of domperidone, whereas CYP3A4, CYP1A2 and CYP2E1 are involved in domperidone aromatic hydroxylation.

Excretion

Urinary and faecal excretions amount to 31 and 66% of the oral dose respectively. The proportion of the drug excreted unchanged is small (10% of faecal excretion and approximately 1% of urinary excretion). The plasma half-life after a single oral dose is 7-9 hours in healthy subjects but is prolonged in patients with severe renal insufficiency. Hepatic impairment

In subjects with moderate hepatic impairment (Pugh score 7 to 9, Child-Pugh rating B), the AUC and C_{max} of domperidone is 2.9- and 1.5-fold higher, respectively, than in healthy subjects. The unbound fraction is increased by 25%, and the terminal elimination half-life is prolonged from 15 to 23 hours. Subjects with mild hepatic impairment have a somewhat lower systemic exposure than healthy subjects based on C_{max} and AUC, with no change in protein binding or terminal half-life. Subjects with severe hepatic impairment were not studied. Prokinin should not be used in patients with moderate or severe hepatic impairment (see section 4.3).

Renal impairment

In subjects with severe renal insufficiency (serum creatinine > 6 mg/100 ml, i.e. > 0.6 mmol/L) the half-life of domperidone is increased from 7.4 to 20.8 hours, but plasma drug levels are lower than in subjects with normal renal function. Very little unchanged drug (approximately 1%) is excreted *via* the kidneys

Paediatric population

No pharmacokinetic data are available in the paediatric population.

5.3 Preclinical safety data

Electrophysiological in vitro and in vivo studies indicate an overall moderate risk of domperidone to prolong the QT interval in humans. In in vitro experiments on isolated cells transfected with HERG and on isolated guinea pig myocytes, exposure ratios ranged between 5 and 30-fold, based on IC50 values inhibiting currents through IKr ion channels in comparison to the free plasma concentrations in humans after administration of the maximum daily dose of 20mg (q.i.d.).

Exposure margins for prolongation of action potential duration in in vitro experiments on isolated cardiac tissues exceeded the free plasma concentrations in humans at maximum daily dose (20mg q.i.d) by 17-fold. However, safety margins in in vitro pro-arrhythmic models (isolated Langendorff perfused heart) and in in vivo models (dog, guinea pig, rabbits sensitised for torsades de pointes) exceeded the free plasma concentrations in humans at maximum daily dose (20mg q.i.d.) by more than 17-fold. In the presence of inhibition of the metabolism via CYP3A4 free plasma concentrations of domperidone can rise up to 10-fold.

At a high, maternally toxic dose (more than 40 times the recommended human dose), teratogenic effects were seen in the rat. No teratogenicity was observed in mice and rabbits.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Methylparaben

Propylparaben

Sorbitol solution

Cremophor RH 40

Saccharin Sodium

Simethicone Emulsion

Microcrystalline Cellulose & Carboxymethyl Cellulose

Liquid Flavor Lemon

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 30 °C.

6.5 Nature and contents of container

180 ml labeled amber colored glass bottle with plastic cap, packed in a printed carton with plastic measuring cup and folded leaflet.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Tabuk Pharmaceutical Manufacturing Company.

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Kingdom of Saudi Arabia

8. MARKETING AUTHORISATION NUMBER(S)

Marketing authorization number in Ethiopia: **08496/08814/NMR/2021**

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorization in Ethiopia: **22/03/2023**

10. DATE OF REVISION OF THE TEXT

August 2023