SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

CINET 1 mg/ml oral suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Composition of the suspension:

Active substance:	
Domperidone	1 mg/ml
Excipients with known effect:	
Sorbitol solution (E420), 70%	455 mg/ml
Methyl para-hydroxybenzoate (E218)	1.8 mg/ml
Propyl para-hydroxybenzoate (E216)	0.2 mg/ml

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral suspension.

White suspension with a sweet flavour.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

CINET is indicated for the relief of the symptoms of nausea and vomiting.

4.2 Posology and method of administration

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

CINET should be taken orally, before meals. If taken after meals, absorption of the medicine will be slightly delayed.

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.

Usually, the maximum treatment duration should not exceed one week.

Posology

Adults and adolescents (aged 12 years and older, and weighing at least 35 kg):
10 ml of oral suspension 1 mg/ml up to three times per day, with a maximum dose of 30 ml per day.

Shake the suspension before use. CINET oral suspension packs contain a 10 ml measuring spoon and a dosing pipette for oral use.

Method of administration

The measuring spoon should be used, i.e. 1 spoon should be taken to make up the 10 ml dose.

Hepatic insufficiency
CINET is contraindicated in case of moderate to severe hepatic insufficiency (see section 4.3). However, no dose adjustment is required in patients with mild hepatic insufficiency (see section 5.2).

Renal insufficiency
Considering that the elimination half-life of domperidone is prolonged in case of severe renal insufficiency, on repeated administration, the dosing frequency should be reduced to once or twice daily, depending on the severity of the impairment. Dose reduction may also be required.

See "Cardiovascular effects", in section 4.4.

4.3 Contraindications

Domperidone is contraindicated in the following situations:
- hypersensitivity to the active substance or to any of the excipients listed in section 6.1;
- prolactin-releasing pituitary tumour (prolactinoma);
- in patients with moderate to severe hepatic insufficiency (see section 5.2);
- in patients with known prolongation of cardiac conduction intervals, particularly QTc, and patients with significant electrolyte disturbances or underlying cardiac diseases, such as congestive heart failure (see section 4.4);
- co-administration with QT-prolonging drugs, excluding apomorphine (see sections 4.4 and 4.5);
- co-administration with potent CYP3A4 inhibitors (irrespective of their QT-prolonging effects) (see section 4.5):
- when stimulation of gastric motility might be harmful: gastrointestinal haemorrhage, mechanical obstruction or perforation.

4.4 Special warnings and precautions for use

Precautions for use

CINET oral suspension contains sorbitol solution (E420). Patients with rare hereditary problems of fructose intolerance should not take this medicine.

CINET contains methyl para-hydroxybenzoate (E218) and propyl para-hydroxybenzoate (E216). It may cause allergic reactions (possibly delayed).

Paediatric population

Undesirable neurological effects are rare (see section 4.8.). Since metabolic functions and the blood-brain barrier are not fully developed in the first months of life, the risk of undesirable neurological effects is higher in younger children.
Excessive dosing may cause extrapyramidal symptoms in children; however, other causes should be taken into consideration.

This medicinal product is not indicated in children under 12 years of age or weighing less than 35 kg.

Renal insufficiency

The elimination half-life of domperidone is prolonged in patients with severe renal insufficiency. In case of repeated administration, the dosing frequency should be reduced to once or twice daily, depending on the severity of the impairment. Dose reduction may also be required.

Cardiovascular effects

Domperidone has been associated with QT interval prolongation on the electrocardiogram. During post-marketing surveillance, very rare cases of QT prolongation and torsade de pointes have been reported 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 have revealed 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 over 60, as well as in patients taking daily doses higher than 30 mg and patients concomitantly taking QT-prolonging drugs or CYP3A4 inhibitors.

Domperidone should be used at the lowest effective dose in adults and adolescents aged 12 years and older and weighing at least 35 kg.

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

Use with apomorphine: Concomitant administration of domperidone and QT-prolonging drugs, including apomorphine, is contraindicated, unless the benefits of co-administration outweigh the associated risks, and only if the recommended precautions for co-administration mentioned in the apomorphine SPC are strictly followed. Please refer to the apomorphine SPC.

Treatment with domperidone should be interrupted if any signs or symptoms that may be associated with cardiac arrhythmia occur, in which case patients should consult their physician.

Patients should be advised to report any cardiac symptoms immediately.

4.5 Interaction with other medicinal products and other forms of interaction

Increased risk of QT prolongation due to pharmacokinetic and/or pharmacodynamic interactions.

Concomitant use of the following substances is contraindicated:

QTc-prolonging medicinal products
- class IA anti-arrhythmics (e.g. disopyramide, hydroquinidine, quinidine)
- class III anti-arrhythmics (e.g. amiodarone, dofetilide, dronedarone, ibutilide, sotalol)
- certain antipsychotics (e.g. haloperidol, pimozide, sertindole)
- certain antidepressants (e.g. citalopram, escitalopram)
- certain antibiotics (e.g. erythromycin, levofloxacin, moxifloxacin, spiramycin)
- certain antifungal agents (e.g. pentamidine)
- certain antimalarial agents (particularly halofantrine and lumefantrine)
- certain gastrointestinal medicines (e.g. cisapride, dolasetron, prucalopride)
- certain antihistamines (e.g. mequitazine, mizolastine)
- certain medicines used to treat cancer (e.g. toremifene, vandetanib, vincamine)
- apomorphine, unless the benefits of co-administration outweigh the risks, and only if the recommended precautions for co-administration are strictly followed. Please refer to the apomorphine SPC.
- certain other medicines (e.g. bepridil, diphemanil, methadone)

(see section 4.3).

Potent CYP3A4 inhibitors (irrespective 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).

Caution is required when the following substances are administered concomitantly
Caution should be taken when administering bradycardia- or hypokalaemia-inducing drugs, or the following macrolides, which are involved in QT prolongation: azithromycin and roxithromycin (clarithromycin is contraindicated, as it is a potent CYP3A4 inhibitor).

The list of substances presented above is representative and not exhaustive.

4.6 Fertility, pregnancy and lactation

Pregnancy

Post-marketing data on the use of domperidone in pregnant women are limited. A study in female rats revealed reproductive toxicity at a high, maternally toxic dose. The potential risk for humans is unknown.

Therefore, CINET should only be used during pregnancy when justified by the anticipated therapeutic benefit.

Breast-feeding

Domperidone is excreted in human milk; however, breastfed infants receive less than 0.1% of the maternal weight-adjusted dose. The occurrence of adverse effects, particularly cardiac effects, following exposure via breast milk, cannot be excluded. 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 mother. Caution should be taken in case of risk factors for QTc prolongation in breastfed infants.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Adverse drug reactions are classified by frequency, using the following convention: very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

Immune system disorders:
Very rare: allergic reactions, including anaphylaxis, anaphylactic shock, anaphylactic reaction, angioedema.

Endocrine disorders:
Rare: increased prolactin levels.

Psychiatric disorders:
Very rare: agitation, nervousness.

Nervous system disorders:
Very rare: undesirable extrapyramidal effects, convulsions, drowsiness, headache.

Cardiac disorders:
Not known: QTc prolongation, ventricular arrhythmias, torsade de pointes, sudden cardiac death (see section 4.4).

Gastrointestinal disorders:
Rare: gastrointestinal disturbances, including intestinal pain, such as temporary colic, very rarely.
Very rare: diarrhoea.

Skin and subcutaneous tissue disorders:
Very rare: urticaria, pruritus, rash.

Reproductive system and breast disorders:
Rare: galactorrhoea, gynaecomastia, amenorrhoea.

Investigations:
Very rare: abnormal liver function tests.

Since the hypophysis is located outside the blood-brain barrier, domperidone may increase prolactin levels. In rare cases, this hyperprolactinaemia can cause undesirable neuroendocrinological effects, such as galactorrhoea, gynaecomastia and amenorrhoea.

Undesirable extrapyramidal effects are very rare in neonates and infants, and exceptional in adults. These undesirable effects resolve spontaneously and completely as soon as treatment is discontinued.

Other effects on the central nervous system, such as convulsions, agitation and drowsiness, are also very rare and primarily reported in infants and children.

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.

4.9 Overdose

Symptoms

Overdose has been reported primarily in infants and children. The symptoms of overdose include agitation, altered consciousness, convulsions, disorientation, drowsiness and extrapyramidal reactions.

Treatment

There is no specific antidote for domperidone. In the event of overdose, gastric lavage, as well as activated charcoal administration, may be useful.

In the event of overdose, standard symptomatic treatment should be immediately initiated. ECG monitoring should be performed, given the possibility of QT interval prolongation. Close medical supervision and supportive therapy are recommended. Anticholinergic anti-Parkinson drugs may be useful to control extrapyramidal reactions.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: 6.3.1. - Digestive system. Modifiers of gastrointestinal motility. Modifiers of gastric motility or prokinetic agents.
ATC Code: A03F A03

Domperidone, the active substance of CINET, is a dopamine antagonist with gastrokinetic and antiemetic properties. Domperidone does not readily cross the blood-brain barrier.

In patients receiving domperidone, extrapyramidal effects are very rare, especially in adults. However, domperidone promotes prolactin release by the pituitary gland.

The antiemetic effect of domperidone may be due to a combination of peripheral effects (gastrokinetic) and dopamine receptor blocking in the chemoreceptor trigger zone, which lies outside the blood-brain barrier, in the area postrema. Studies in animals have revealed low domperidone levels in the brain, as well as a predominantly peripheral effect of domperidone on dopamine receptors. Studies in humans have shown that orally administered domperidone increases oesophageal pressure, improves antroduodenal motility and speeds up gastric emptying. Domperidone has no effect on gastric secretion.

According to ICH - E14 guidelines, a thorough study of the QT interval was conducted. This study included a placebo, an active comparator and a positive control, and was conducted in healthy volunteers receiving up to 80 mg of domperidone daily, administered as four 10 mg or 20 mg doses per day. This study detected a maximal difference in LS means for QTc change from baseline between domperidone and placebo of 3.4 ms in subjects receiving a daily dose of 20 mg of domperidone, administered four times a day, on Day 4. The 2-sided 90% CI (1.0 to 5.9 ms) did not exceed 10 ms. No clinically relevant QTc effects were observed in this study with domperidone doses up to 80 mg/day (i.e. more than twice the maximum recommended dose).

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

5.2 Pharmacokinetic properties

Absorption

Domperidone is rapidly absorbed after oral administration. Peak plasma concentrations are reached approximately 1 hour after administration. Cmax and AUC increased proportionally with the domperidone dose in the 10-20 mg range. A 2- to 3-fold increase in AUC was observed with repeated dosing (four times daily, every 5 hours, for 4 days).

Although bioavailability is enhanced in normal subjects when domperidone is taken after a meal, patients with gastrointestinal complaints should take domperidone 15-30 minutes before a meal. Reduced gastric acidity impairs domperidone absorption. Oral bioavailability is decreased by prior concomitant administration of cimetidine and sodium bicarbonate.

Distribution

Oral domperidone does not appear to accumulate or induce its own metabolism. After two weeks of oral administration of 30 mg of domperidone per day, a peak plasma concentration of 21 ng/ml was reached 90 minutes after administration, which is almost identical to the 18 ng/ml measured after the first administration.

Domperidone is 91-93% bound to plasma proteins. Distribution studies with radioactively labelled domperidone in animals revealed an extensive distribution of the drug in tissues, although brain concentrations were low. Studies in female rats have revealed that small quantities of the drug cross the placental barrier.

Biotransformation

Domperidone undergoes fast, extensive hepatic metabolization through hydroxylation and N-dealkylation. *In vitro* metabolism experiments with diagnostic inhibitors have revealed that CYP3A4 is the primary form of cytochrome P450 involved in domperidone N-dealkylation, whereas CYP3A4, CYP1A2 and CYP2E1 are involved in the aromatic hydroxylation of domperidone.

Elimination

About 31% and 55% of the orally administered dose are eliminated in the urine and faeces, respectively. The proportion of unchanged excreted drug is small (10% of faecal excretion and approximately 1% of urinary excretion).

Plasma half-life following oral administration of a single dose is 7-9 hours in healthy volunteers, but is prolonged in patients with severe renal insufficiency.

Hepatic insufficiency

In patients with moderate hepatic insufficiency (Pugh score 7-9; Child-Pugh grade B), the AUC and Cmax of domperidone are 2.9 and 1.5 times higher than those observed in healthy subjects, respectively.

The unbound fraction is increased by 25% and the terminal elimination half-life is prolonged from 15 to 23 hours. Systemic exposure is somewhat lower in patients with mild hepatic insufficiency, based on Cmax and AUC values, although no changes in protein binding or terminal half-life are observed.

No studies have been conducted in patients with severe hepatic insufficiency. Domperidone is contraindicated in patients with moderate to severe hepatic insufficiency (see section 4.3).

Renal insufficiency

In patients with severe renal insufficiency (creatinine clearance <30 ml/min/1.73 m2), the elimination half-life of domperidone increased from 7.4 to 20.8 hours, but plasma levels were lower than in healthy volunteers.

As only a small percentage of the unchanged drug (approximately 1%) is excreted via the kidneys, adjustment of a single dose in patients with renal insufficiency is unlikely to be required.

However, on repeated administration, the dosing frequency should be reduced to once or twice daily, depending on the severity of the impairment. Dose reduction may also be required.

5.3 Preclinical safety data

Electrophysiological *in vitro* and *in vivo* studies indicate an overall moderate risk of QTc interval prolongation in humans. In *in vitro* experiments on isolated cells transfected with hERG and isolated guinea pig myocytes, exposure ratios ranged between 26- and 47-fold, based on IC50 values determined for IKr ion channel current inhibition, compared with free plasma concentrations in humans after administration of the maximum daily dose of 10 mg, administered 3 times a day. Safety margins for prolongation of action potential duration in *in vitro* experiments on isolated cardiac tissues exceeded free plasma concentrations in humans receiving the maximum daily dose (10 mg, administered 3 times a day) by 45-fold. Safety margins in *in vitro* proarrhythmic models (isolated Langendorff perfused heart) exceeded free plasma concentrations in humans receiving the maximum daily dose (10 mg, administered 3 times a day) by 9- to 45-fold. In *in vivo* models, no-effect levels for QTc prolongation in dogs and induction of arrhythmias in a rabbit model sensitised for torsade de pointes exceeded free plasma concentrations in humans receiving the maximum daily dose (10 mg, administered 3 times a day) by more than 22-fold and 435-fold, respectively. In the anesthetised guinea pig model following slow intravenous infusions, no effects on QTc were observed at total plasma concentrations of 45.4 ng/ml, i.e. 3 times higher than total plasma levels in humans receiving the maximum daily dose (10 mg, administered 3 times a day). The relevance of the latter study for humans following exposure to orally administered domperidone is unknown.

In case of inhibition of metabolism via CYP3A4, free plasma concentrations of domperidone can increase up to 3-fold.

Teratogenic effects were observed in rats at a high maternally toxic dose (more than 40 times the recommended dose in humans). No teratogenicity was observed in mice and rabbits.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Polysorbate 20, microcrystalline cellulose and sodium carboxymethyl cellulose, sorbitol solution (E420) 70%, methyl para-hydroxybenzoate (E218), propyl para-hydroxybenzoate (E216), sodium saccharin (E954) and purified water.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.
Shelf life after first opening the container: 12 months

6.4 Special precautions for storage

Do not store above 30ºC.

Keep the bottle tightly closed.

6.5 Nature and contents of container

The oral suspension is stored in type III amber glass bottles with polyethylene cap.

Each bottle contains 100 ml or 200 ml. Each bottle is packed in a suitable carton, together with the corresponding information leaflet, a 10 ml measuring spoon and a dosing pipette for oral use.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

01/2022