SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

MOTIS 10 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:
Domperidone maleate……..12.72 mg (equivalent to 10 mg domperidone)

Excipient(s) with known effect:
Lactose monohydrate (from bovine milk)……..54.48 mg
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet
White, round, biconvex tablets debossed with "Dm 10" on one side.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

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

4.2. Posology and method of administration

Posology/Frequency and duration of administration:
Adults and adolescents:
For the indication of nausea and vomiting: It should be used as 3x10 mg/day provided that duration does not exceed 7 days.

Adults and children should be used at the lowest effective dose possible. Because taking doses above 30 mg daily or using it in elderly patients over 60 years of age may increase the possibility of serious ventricular arrhythmia or sudden cardiac death.

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

Method of administration
MOTIS should be used at the lowest effective dose for the shortest duration necessary to control nausea and vomiting. It is recommended to take MOTIS orally before meals. If taken after meals, absorption of the drug is somewhat 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.

Additional information on special populations:
Renal/Hepatic impairment
MOTIS 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). Since the elimination half-life of domperidone is prolonged in severe renal impairment, on repeated administration, the dosing frequency of MOTIS should be reduced to once or twice daily depending on the severity of the impairment.

Pediatric population
It should be used in the lowest effective dose possible.
Tablets are not suitable for children under 35 kg due to the need for appropriate dosing. The use of oral suspension is recommended in these patients.

Geriatric population
Elderly patients over 60 years of age may be more likely to have serious ventricular arrhythmias or sudden cardiac death.

4.3. Contraindications

MOTIS is contraindicated in the following situations:
- Known hypersensitivity to domperidone or any of the excipients.
- Prolactin-releasing pituitary tumour (prolactinoma).
- In cases where increased gastric motility may be dangerous, such as gastrointestinal bleeding, mechanical obstruction or perforation
- In patients with moderate or severe hepatic impairment (see section 5.2).
- In patients who have known existing prolongation of cardiac conduction intervals, particularly QTc, patients with significant electrolyte disturbances or underlying cardiac diseases such as congestive heart failure (see section 4.4).
- Co-administration with QT-prolonging drugs (see section 4.5).
- Co-administration with potent CYP3A4 inhibitors (regardless of their QT prolonging effects) (see section 4.5).

4.4. Special warnings and precautions for use

Use in patients with renal impairment
Since the elimination half-life of domperidone is prolonged in severe renal impairment, the dosing frequency of domperidone should be reduced to once or twice daily depending on the severity of the impairment in repeated administration.

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).

Some epidemiological studies showed that domperidone was associated with an increased risk of serious ventricular arrhythmias or sudden cardiac death (see section 4.8). This risk may be higher in patients aged 60 years and over or in use of daily doses more than 30 mg. Therefore, domperidone should be used at the lowest effective dose possible.

It should be used with caution in patients with cardiac causes prolonging QT and electrolyte disturbances. (see section 4.5)

MOTIS 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 (hypokalemia, hyperkalemia, hypomagnesemia), 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 (hypokalemia, hyperkalemia, hypomagnesemia) 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 promptly consult their physician.

Patients should be advised to promptly report any cardiac symptoms.

Pediatric population
Although neurological side effects are rare (see section 4.8), the risk of neurological side effects is high in young children, since metabolic functions and the blood-brain barrier are not fully developed in the first months of life. Therefore, accurate dosing and close monitoring in neonates, infants and children are recommended (see section 4.2).

Overdose may cause extrapyramidal symptoms in children, but other conditions should also be considered.

MOTIS tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5. Interaction with other medicinal products and other forms of interaction

When antacids and antisecretory drugs are used concomitantly with MOTIS, they should be taken after meals, not before. These drugs should not be taken at the same time as domperidone suspensions.

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

The main metabolic pathway of domperidone is CYP3A4. Data from *in vitro* and human studies have shown that concomitant use of drugs that significantly inhibit this enzyme may result in increased plasma levels of domperidone.

Due to pharmacodynamic and/or pharmacokinetic interactions, the risk of QT interval prolongation is increased.

Concomitant use with the following medicines is contraindicated:
QTc-prolonging medicinal products (risk of torsades de points)
- Anti-arrhythmics class IA (disopyramide, hydroquinidine, quinidine)
- Anti-arrhythmics class III (amiodarone, dofetilide, dronedarone, ibutilide, sotalol)
- Certain antipsychotics (haloperidol, pimozide, sertindole)
- Certain antidepressants (citalopram, escitalopram)

- Certain antibiotics (erythromycin, levofloxacin, moxifloxacin, spiramycin)
- Certain antifungal agents (fluconazole, pentamidine)
- Certain antimalarial agents (in particular halofantrine, lumefantrine)
- Certain gastro-intestinal medicines (cisapride, dolasetron, prucalopride)
- Certain antihistaminics (mequitazine, mizolastine)
- Certain medicines used in cancer (toremifene, vandetanib, vincamine)
- Certain other medicines (bepridil, diphemanil, methadone)

Potent CYP3A4 inhibitors (regardless of their QT prolonging effects)
- Protease inhibitors (ritonavir, saquinavir, telaprevir)
- Systemic azole antifungals (itraconazole, ketoconazole, posaconazole, voriconazole)
- Certain macrolide antibiotics (clarithromycin, telithromycin, erythromycin) (see section 4.3).

Concomitant use with the following medicines is not recommended:
- Moderate CYP3A4 inhibitors (diltiazem, verapamil and some macrolides)

Concomitant use with the following medicines requires caution:
Medicines that induce bradycardia and hypokalemia, as well as with macrolides that prolong the QT interval, such as azithromycin and roxithromycin (clarithromycin is contraindicated because it is a potent CYP3A4 inhibitor).

The above list of medicines is representative and not exhaustive.

4.6. Fertility, pregnancy and lactation

General recommendation
Pregnancy category: C

Women of childbearing potential / Contraception
There are insufficient data to indicate the need for contraception regarding MOTIS in women of childbearing potential.

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). The potential risk to humans is unknown. Therefore, MOTIS should only be used during pregnancy when justified by the anticipated therapeutic benefit.

Breastfeeding
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 continue domperidone therapy or to continue breastfeeding, taking into account the benefit of treatment for women and the benefit of breastfeeding for children. Caution should be exercised in case of QTc prolongation risk factors in breast-fed infants.

Reproductive ability / Fertility
A study in rats showed reproductive toxicity at high toxic doses taken by the mother.

4.7. Effects on ability to drive and use machines

Dizziness and somnolence have been observed following use of domperidone (see section 4.8) therefore, patients should be advised not to drive or use machinery or engage in other activities requiring mental alertness and coordination until they have established how MOTIS affects them.

4.8. Undesirable effects

The safety of domperidone was evaluated in 1275 patients with dyspepsia, gastro-esophageal reflux disorder (GERD), 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 domperidone. 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.

Adverse drug reaction frequencies are evaluated according to the following criteria:
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)

Immune system disorders
Not known: Anaphylactic reaction (including anaphylactic shock)

Psychiatric disorders
Uncommon: Loss of libido, anxiety, agitation, nervousness

Nervous system disorders
Uncommon: Dizziness, somnolence, headache, extrapyramidal disorder
Not known: Convulsion, restless leg syndrome

Eye disorders
Not known: Oculogyric crisis

Cardiac disorders
Not known: Ventricular arrhythmias, sudden cardiac death, QTc prolongation, *Torsade de Pointes* (see section 4.4)

Gastrointestinal disorders
Common: Dry mouth
Uncommon: Diarrhea

Skin and subcutaneous tissue disorder
Uncommon: Rash, pruritus, urticaria
Not known: Angioedema

Renal and urinary disorders
Not known: Urinary retention

Reproductive system and breast disorders
Uncommon: Galactorrhea, breast pain, breast tenderness
Not known: Gynecomastia, amenorrhea

General disorders and administration site conditions
Uncommon: Asthenia

Investigations
Not known: Liver function test abnormal, blood prolactin increased

In 45 clinical 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.

Extrapyramidal disorder occurs mainly in newborns and infants.

Other central nervous system-related convulsive and agitation effects have also been reported, primarily in newborn infants and children.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization 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 reporting system.

4.9. Overdose

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

Treatment
There is no specific antidote to domperidone, but in the event of overdose, standard symptomatic treatment should be given immediately. ECG monitoring should be undertaken, because of the possibility of QT interval prolongation. The administration of activated charcoal as well as gastric lavage may be useful.

There is no specific antidote to domperidone; but in the event of a large overdose, gastric lavage within one hour of ingestion as well as the administration of activated charcoal may be useful. Close medical supervision and supportive therapy are recommended. Anticholinergic, anti-parkinson drugs may be helpful in controlling the extrapyramidal reactions.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used for functional gastrointestinal disorders, prokinetics
ATC code: A03FA03

Domperidone is a dopamine antagonist with anti-emetic properties. Domperidone does not readily cross the blood-brain barrier. In domperidone users, especially adults, extrapyramidal side effects are very rare, but domperidone promotes the release of prolactin from the pituitary. Its anti-emetic 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 esophageal pressure, improve antroduodenal motility and accelerate gastric emptying. There is no effect on gastric secretion.

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 LS-means 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 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

General properties

Absorption

Domperidone is rapidly absorbed after oral administration, with peak plasma concentrations, occurring at approximately 1 hour after dosing. The C_{max} and AUC values of domperidone increased proportionally with dose in the 10 mg to 20 mg dose range. A 2- to 3-fold accumulation of domperidone AUC was observed with repeated four times daily (every 5 hr) dosing of domperidone for 4 days.

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.

Distribution

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

Domperidone undergoes rapid and extensive hepatic metabolism by hydroxylation and N-dealkylation. 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.

Elimination

Urinary and fecal excretions amount to 31 and 66% of the oral dose respectively. The proportion of the drug excreted unchanged is small (10% of fecal 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.

Linearity/Nonlinearity:
There is no information about linearity/non-linearity.

Additional information on special populations
Renal impairment
In subjects with severe renal insufficiency (creatinine clearance <30 ml/min/1.73m^2) the elimination half-life of domperidone was increased from 7.4 to 20.8 hours, but plasma drug levels were lower than in healthy volunteers. Since very little unchanged drug (approximately 1%) is excreted via the kidneys, it is unlikely that the dose of a single administration needs to be adjusted in patients with renal insufficiency. However, on repeated administration, the dosing frequency should be reduced to once or twice daily depending on the severity of the impairment, and the dose may need to be reduced.

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. Domperidone is contraindicated in patients with moderate or severe hepatic impairment (see section 4.3).

Pediatric patients
No pharmacokinetic data are available in the pediatric population.

5.3. Preclinical safety data

Electrophysiological *in vitro* and *in vivo* studies indicate an overall moderate risk of domperidone to prolong the QTc interval in humans.

In in-vitro experiments on isolated cells transfected with hERG and on isolated guinea pig myocytes, exposure ratios ranged between 26- 47-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 10mg administered 3 times a day. Safety margins for prolongation of action potential duration *in-vitro* experiments on isolated cardiac tissues exceeded the free plasma concentrations in humans at maximum daily dose (10mg administered 3 times a day.) by 45 fold. Safety margins in *in-vitro* proarrhythmic models (isolated Langendorff perfused heart) exceeded the free plasma concentrations in humans at maximum daily dose (10mg administered 3 times a day) by 9- up to 45-fold. In *in-vivo* models the no-effect levels for QTc prolongation in dogs and induction of arrhythmias in rabbit model sensitized for torsade de pointes exceeded the free plasma concentrations in humans at maximum daily dose (10mg administered 3 times a day) by more than 22-fold and 435-fold, respectively. In the anesthetized guinea pig model following slow intravenous infusions, there were no effects on QTc at total plasma concentrations of 45.4 ng/mL, which are 3-fold higher than the total plasma levels in humans at maximum daily dose (10mg administered 3 times a day). The relevance of the latter study for humans following exposure to orally administered domperidone is uncertain.

In the presence of inhibition of the metabolism via CYP3A4 free plasma concentrations of domperidone can rise up to 3-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

Lactose monohydrate (produced from bovine milk)
Maize starch
Povidone
Sodium lauryl sulfate
Microcrystalline cellulose
Anhydrous colloidal silica
Magnesium stearate

6.2. Incompatibilities

There is no known incompatibility.

6.3. Shelf life

36 months

6.4. Special precautions for storage

Store at room temperature below 25°C protected from moisture and in its original package.

6.5. Nature and contents of container

21 tablets in a transparent PVC/Al blister in a box.

6.6. Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements. This medicinal product may pose a risk to the aquatic environment.

7. MARKETING AUTHORISATION HOLDER

DEVA Holding A.Ş.
Halkalı Merkez Mah. Basın Ekspres Cad. No:1
34303 Küçükçekmece - ISTANBUL/TURKEY

8. MARKETING AUTHORISATION NUMBER

229/33

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorization : 21.01.2011
Date of last renewal :

10. DATE OF REVISION OF THE TEXT

21.03.2019