# Annex III

## Amendments to relevant sections of the summary of product characteristics and package leaflet

Note:

This Summary of Product Characteristics and package leaflet is the outcome of the referral procedure.

The product information may be subsequently updated by the Member State competent authorities, in liaison with the Reference Member State, as appropriate, in accordance with the procedures laid down in Chapter 4 of Title III of Directive 2001/83/EC.

## 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.

*[Throughout the document, whenever references are made to a particular pharmaceutical formulation they should only be implemented where the said formulation is authorised]*

### Section 4.1 Therapeutic indications

*[The wording of this section should read as follows:]*

{X} is indicated for the relief of the symptoms of nausea and vomiting.

### Section 4.2 Posology and method of administration

*[This section should be amended to reflect the following wording, as applicable:]*

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

*[For oral formulations]:* It is recommended to take oral <X> 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.

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

<u>Adults, and adolescents (12 years of age and older and weighing 35 kg or more)</u>

*[Tablets (Film-coated, Coated, Scored coated, Effervescent, Chewable), Orodispersible tablets, capsules]*

One 10 mg tablet up to three times per day with a maximum dose of 30 mg per day.

*[Orodispersible tablets]*

The orodispersible tablet dissolves rapidly in the mouth with the help of the saliva, and the can be taken with or without water. When taken without water, the tablet should be placed on the tongue and dissolve in the mouth before swallowing. If convenient, a glass of water can be taken afterwards.

*[Oral suspension/syrup]*

10 ml (of 1 mg/ml oral suspension) up to three times per day with a maximum dose of 30 ml per day.

*[Effervescent granules 5 mg]*

One or two sachet(s) (containing 5 mg domperidone per sachet) up to three times per day with a maximum dose of 6 sachets per day.

*[Effervescent granules 10 mg]*

One sachet (containing 10 mg domperidone per sachet) up to three times per day with a maximum dose of 3 sachets per day.

*[Suppositories]*

One 30 mg suppository inserted into the rectum two times per day.

*[The paragraph below is to be implemented where the marketing authorisation currently includes relief of the symptoms of nausea and vomiting in children under 12 years of age and adolescents weighing less than 35 kg:]*

Neonates, infants, children (less than 12 years of age) and adolescents weighing less than 35 kg

*Oral Suspension/syrup*

The dose is 0.25 mg/kg. This should be given up to three times per day with a maximum dose of 0.75 mg/kg per day. For example, for a child weighing 10 kg, the dose is 2.5 mg and this can be given three times per day to a maximum dose of 7.5 mg per day.

Oral domperidone should be taken before meals/feeding. If taken after meals absorption of the drug is somewhat delayed.

*Tablets, Effervescent granules, Suppositories*

Due to the need for accurate dosing, tablets, effervescent granules and suppositories are unsuitable for use in children and adolescents weighing less than 35 kg.

Hepatic Impairment

<X> 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 <X> should be reduced to once or twice daily depending on the severity of the impairment, and the dose may need to be reduced.

**Section 4.3 Contraindications**

*[This section should be amended to include the following contraindications]*

Domperidone is contraindicated in the following situations:

- …
- 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)

**Section 4.4 Special warnings and precautions for use**

*[This section should be amended to include the following wording]*

Renal Impairment

The elimination half-life of domperidone is prolonged in severe renal impairment. For repeated administration, the dosing frequency of domperidone should be reduced to once or twice daily depending on the severity of the impairment. The dose may also need to be reduced.

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 30 mg, 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.

**Section 4.5 Interaction with other medicinal products and other forms of interaction**

*[This section should be amended to include the following wording]*

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

**Concomitant use of the following substances is contraindicated**

QTc-prolonging medicinal products

- o anti-arrhythmics class IA (e.g., disopyramide, hydroquinidine, quinidine)
- o anti-arrhythmics class III (e.g., amiodarone, dofetilide, dronedarone, ibutilide, sotalol)

- o certain antipsychotics (e.g., haloperidol, pimozide, sertindole)
- o certain antidepressants (e.g., citalopram, escitalopram)
- o certain antibiotics (e.g. , erythromycin, levofloxacin, moxifloxacin, spiramycin)
- o certain antifungal agents (e.g., pentamidine)
- o certain antimalarial agents (in particular halofantrine, lumefantrine)
- o certain gastro-intestinal medicines (e.g., cisapride, dolasetron, prucalopride)
- o certain antihistaminics (e.g., mequitazine, mizolastine)
- o certain medicines used in cancer (e.g., toremifene, vandetanib, vincamine)
- o certain other medicines (e.g., bepridil, diphemanil, methadone)

(see section 4.3).

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

- o protease inhibitors
- o systemic azole antifungals
- o 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 contra-indicated as it is a potent CYP3A4 inhibitor).

The above list of substances is representative and not exhaustive.

**Section 4.6 Fertility, pregnancy and lactation**

*[This section should be amended to include the following wording]*

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.

**Section 4.8 Undesirable effects**

*[This following wording should be reflected in this section]*

Cardiac disorders

Not known: ventricular arrhythmias, QTc prolongation, Torsade de Pointes, sudden cardiac death (see section 4.4)

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 reporting system listed in Appendix V.

**Section 4.9 Overdose**

*[This following wording should be reflected in this section]*

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.

**Section 5.1 Pharmacodynamic properties**

*[This following wording should be reflected in this section]*

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 (1.0 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.

**Section 5.2 Pharmacokinetic properties**

*[This section should be amended to include the following wording]*

Absorption

Domperidone is rapidly absorbed after oral administration, with peak plasma concentrations occurring at approximately 1 hr after dosing. The Cmax 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.

Hepatic impairment

In subjects with moderate hepatic impairment (Pugh score 7 to 9, Child-Pugh rating B), the AUC and Cmax 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 Cmax 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).

Renal impairment

In subjects with severe renal insufficiency (creatinine clearance<30 ml/min/1.73m2) 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.

**Section 5.3 Preclinical safety data**

*[This section should be amended to include the following wording]*

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 10 mg administered 3 times a day. Safety 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 (10 mg 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 (10 mg 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 a rabbit model sensitized for torsade de pointes exceeded the free plasma concentrations in humans at maximum daily dose (10 mg 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 ~~at~~ in humans at 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 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

**PACKAGE LEAFLET**

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

**Section 1 'What X is and what it is used for'**

*[This section should be amended to include the below wording]*

This medicine is used in adults and in children to treat nausea (feeling sick) and vomiting (being sick).

**Section 2 'What you need to know before you take X '**

*[This section should be amended to include the below wording]*

Do not take <X>:- if you have a moderate or severe liver disease

- if your ECG (electrocardiogram) shows a heart problem called "prolonged QT corrected interval"

- if you have or had a problem where your heart cannot pump the blood round your body as well as it should (condition called heart failure).

- if you have a problem that gives you a low level of potassium or magnesium, or a high level of potassium in your blood.

- if you are taking certain medicines (see "Taking other medicines")

**Warnings and precautions**

Before taking this medicine contact your doctor if you:

- suffer from liver problems (liver function impairment or failure) (see "Do not take this medicinal product")

- suffer from kidney problems (kidney function impairment or failure). It is advisable to ask your doctor for advice in case of prolonged treatment as you may need to take a lower dose or take this medicine less often, and your doctor may want to examine you regularly.

Domperidone may be associated with an increased risk of heart rhythm disorder and cardiac arrest. This risk may be more likely in those over 60 years old or taking doses higher than 30mg per day. The risk also increases when domperidone is given together with some drugs. Tell your doctor or pharmacist if you are taking drugs to treat infection (fungal infections or bacterial infection) and/or if you have heart problems or AIDS/HIV (see section other medicines and X).

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

While taking domperidone, contact your doctor if you experience heart rhythm disorders such as palpitations, trouble breathing, loss of consciousness. Treatment with domperidone should be stopped.

**Other medicines and X**

Do not take {Product Name} if you are taking medicine to treat:

- fungal infections such as azole anti-fungals, specifically oral ketoconazole, fluconazole or voriconazole
- bacterial infections, specifically erythromycin, clarithromycin, telithromycin, moxifloxacin, pentamidine (these are antibiotics)
- heart problems or high blood pressure (e.g., amiodarone, dronedarone, quinidine, disopyramide, dofetilide, sotalol, diltiazem, verapamil)
- psychoses (e.g., haloperidol, pimozide, sertindole)
- depression (e.g., citalopram, escitalopram)
- gastro-intestinal disorders (e.g., cisapride, dolasetron, prucalopride)
- allergy (e.g., mequitazine, mizolastine)
- malaria (in particular halofantrine)
- AIDS/HIV (protease inhibitors)
- cancer (e.g., toremifene, vandetanib, vincamine)

Tell your doctor or pharmacist if you are taking drugs to treat infection, heart problems or AIDS/HIV.

It is important to ask your doctor or pharmacist if {Tradename} is safe for you when you are taking any other medicines, including medicines obtained without prescription.

**Breast-feeding**

Small amounts of domperidone have been detected in breast milk. Domperidone may cause unwanted side effects affecting the heart in a breast-fed baby. Domperidone should be used during breast feeding only if your physician considers this clearly necessary. Ask your doctor for advice before taking this medicine.

**Section 3 'How to take X'**

*[This section should be amended to include the below wording]*

Follow these instructions closely unless your doctor has advised you otherwise.

**Duration of treatment:**

Symptoms usually resolve with 3-4 days of taking this medicine. Do not take {Tradename} for longer than 7 days without consulting your doctor.

**Adults and adolescents <u>12 years of age and older</u> with a body weight of 35 kg or more**

*Tablets 10 mg*

[*Instructions for use must be included*]

The usual dose is one tablet taken up to three times per day, if possible before meals.

Do not take more than three tablets per day.

*Orodispersible tablets 10 mg*

[*Instructions for use must be included*]

The usual dose is one tablet taken up to three times per day, if possible before meals.

Do not take more than three tablets per day.

*Oral suspension*

[*Appropriate measure device such as dosing cup must be provided with the product, and*

*instructions for use must be included*]

The usual dose is 10 mg taken up to three times per day, if possible before meals. Do not take more than 30 mg per day.

*Effervescent granules 5 mg*

[*Instructions for use must be included*]

The usual dose is one or two sachet(s) (with 5 mg domperidone per sachet) taken up to three times per day. Do not take more than six sachets per day.

*Effervescent granules 10 mg*

[*Instructions for use must be included*]

The usual dose is one sachet (with 10 mg domperidone per sachet) taken up to three times per day. Do not take more than three sachets per day.

*Suppositories 30 mg*

*[Instructions for use must be included]*

The usual dose is one suppository two times a day. Do not use more than two suppositories per day.

*[The paragraph below is to be implemented where the marketing authorisation currently includes relief of the symptoms of nausea and vomiting in children under 12 years of age and adolescents weighing less than 35 kg:]*

**Children and adolescents from birth to a body weight of less than 35 kg**

*Oral suspension*

[*Graduated oral syringe must be provided with the product, and instructions for use must be included*]

Give the dose maximum 3 times a day, if possible before meals/feeding. Do not give more than 3 times in a 24 hour time period.

<Tablets>, <orodispersible tablets> and <suppositories>are not suitable for children weighing less than 35 kg.

If {Product name} is for a child, ask your doctor for the children's formulation.

**If you take more X than you should**

If you have used or taken too much {Tradename}, contact your doctor, pharmacist or the poison centre immediately, in particular if a child has taken too much. In the event of overdose, symptomatic treatment could be implemented. An ECG monitoring could be undertaken, because of the possibility of a heart problem called prolonged QT interval.

**If you forget to take X**

Take your medicine as soon as you remember. If it is almost time for your next dose, wait until that is due and then continue as normal. Do not take a double dose to make up for a forgotten dose.

**Section 4 Possible side effects**

**Not known** (frequency cannot be estimated from the available data)

Disorders of the cardiovascular system: heart rhythm disorders (rapid or irregular heart beat) have been reported; if this happens, you should stop the treatment immediately. Domperidone may be associated with an increased risk of heart rhythm disorder and cardiac arrest. This risk may be more likely in those over 60 years old or taking doses higher than 30 mg per day. Domperidone should be used at the lowest effective dose in adults and children.

**Reporting of side effects**

If you get any side effects, talk to your <doctor> <or> <,> <pharmacist> <or nurse>. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V*. By reporting side effects you can help provide more information on the safety of this medicine.