# ANNEX III

# SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET

# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. NAME OF THE MEDICINAL PRODUCT

Kytril and associated names (see Annex I) 1 mg film-coated tablets
Kytril and associated names (see Annex I) 2 mg film-coated tablets
[See Annex I - To be completed nationally]

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

### 2.1 General description

### 2.2 Qualitative and quantitative composition

Each film-coated tablet contains 1 mg granisetron (as the hydrochloride).
Each film-coated tablet contains 2 mg granisetron (as the hydrochloride).

*Excipients*

Each tablet contains 69.38 mg of lactose monohydrate.
Each tablet contains 138.76 mg of lactose monohydrate.

For a full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Film-coated tablet.
The tablets are white to almost white triangular biconvex tablets imprinted with K1 on one side.
The tablets are white to almost white triangular biconvex tablets imprinted with K2 on one side.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Kytril film-coated tablets are indicated in adults for the prevention and treatment of acute nausea and vomiting associated with chemotherapy and radiotherapy.

Kytril film-coated tablets are indicated in adults for prevention of delayed nausea and vomiting associated with chemotherapy and radiotherapy.

### 4.2 Posology and method of administration

Posology

1 mg twice a day or 2 mg once a day for up to one week following radiotherapy or chemotherapy.
The first dose of Kytril should be administered within 1 hour before the start of therapy.
Dexamethasone has been used concomitantly at doses up to 20 mg once a day orally.

*Paediatric population*

The safety and efficacy of granisetron tablets in children have not yet been established.
No data are available.

*Elderly and renal impairment*

There are no special precautions required for its use in either elderly patients or those patients with renal or hepatic impairment.

*Hepatic impairment*

There is no evidence to date for an increased incidence of adverse events in patients with hepatic disorders. On the basis of its kinetics, whilst no dosage adjustment is necessary, granisetron should be used with a certain amount of caution in this patient group (see section 5.2).

Method of administration

The tablets should be swallowed whole with water.

## 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

## 4.4 Special warnings and precautions for use

As granisetron may reduce lower bowel motility, patients with signs of sub-acute intestinal obstruction should be monitored following its administration.

As for other 5-$HT_3$ antagonists, ECG changes including QT interval prolongation have been reported with granisetron. In patients with pre-existing arrhythmias or cardiac conduction disorders this might lead to clinical consequences. Therefore caution should be exercised in patients with cardiac co-morbidities, on cardiotoxic chemotherapy and/or with concomitant electrolyte abnormalities (see section 4.5).

Cross-sensitivity between 5-$HT_3$ antagonists (e.g. dolasteron, ondansetron) has been reported.

Patients with rare hereditary problems of galactose intolerance, lactase deficiency or glucose-galactose malabsorption should not take this medicine.

*Paediatric population*

There is insufficient clinical evidence to recommend administration of these tablets to children.

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

As for other 5-$HT_3$ antagonists, cases of ECG modifications including QT prolongation have been reported with granisetron. In patients concurrently treated with medicinal products known to prolong QT interval and/or which are arrhythmogenic, this may lead to clinical consequences (see section 4.4).

In studies in healthy subjects, no evidence of any interaction has been indicated between granisetron and benzodiazepines (lorazepam), neuroleptics (haloperidol) or anti-ulcer medicinal products (cimetidine). Additionally, granisetron has not shown any apparent medicinal product interaction with emetogenic cancer chemotherapies.

No specific interaction studies have been conducted in anaesthetised patients.

## 4.6 Fertility, pregnancy and lactation

Pregnancy

There is limited amount of data from the use of granisetron in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). As a precautionary measure**,** it is preferable to avoid the use of granisetron during pregnancy.

Breastfeeding

It is unknown whether granisetron or its metabolites are excreted in human milk. As a precautionary measure, breast-feeding should not be advised during treatment with Kytril.

Fertility

In rats, granisetron had no harmful effects on reproductive performance or fertility.

## 4.7 Effects on ability to drive and use machines

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

## 4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse reactions for Kytril are headache and constipation, which may be transient. ECG changes including QT prolongation have been reported with Kytril (see sections 4.4 and 4.5).

Tabulated list of adverse reactions

The following table of listed adverse reactions is derived from clinical trials and post-marketing data associated with Kytril and other 5-$HT_3$ antagonists.

Frequency categories are as follows:
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)

| | |
|---|---|
| ***Immune system disorders*** | |
| *Uncommon* | Hypersensitivity reactions e.g. anaphylaxis, urticaria |
| ***Psychiatric disorders*** | |
| *Common* | Insomnia |
| ***Nervous system disorders*** | |
| *Very common* | Headache |
| *Uncommon* | Extrapyramidal Reactions |
| ***Cardiac disorders*** | |
| *Uncommon* | QT prolongation |
| ***Gastrointestinal disorders*** | |
| *Very common* | Constipation |
| *Common* | Diarrhoea |
| ***Hepatobiliary disorders*** | |
| *Common* | Elevated hepatic transaminases* |
| ***Skin and subcutaneous tissue disorders*** | |
| *Uncommon* | Rash |

*Occurred at a similar frequency in patients receiving comparator therapy

Description of selected adverse reactions

As for other 5-$HT_3$ antagonists, ECG changes including QT prolongation have been reported with granisetron (see sections 4.4 and 4.5).

### 4.9 Overdose

There is no specific antidote for Kytril. In the case of overdose with the tablets, symptomatic treatment should be given. Doses of up to 38.5 mg of Kytril as a single injection have been reported, with symptoms of mild headache but no other reported sequelae.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiemetics and antinauseants, Serotonin (5HT3) antagonists.
ATC code: A04AA02.

Neurological mechanisms, serotonin-mediated nausea and vomiting

Serotonin is the main neurotransmitter responsible for emesis after chemo- or radio-therapy. The 5-$HT_3$ receptors are located in three sites: vagal nerve terminals in the gastrointestinal tract and chemoreceptor trigger zones located in the *area postrema* and the *nucleus tractus solidarius* of the vomiting center in the brainstem. The chemoreceptor trigger zones are located at the caudal end of the fourth ventricle (*area postrema*). This structure lacks an effective blood-brain barrier, and will detect emetic agents in both the systemic circulation and the cerebrospinal fluid. The vomiting centre is located in the brainstem medullary structures. It receives major inputs from the chemoreceptor trigger zones, and a vagal and sympathetic input from the gut.

Following exposure to radiation or catotoxic substances, serotonin (5-HT) is released from enterochromaffine cells in the small intestinal mucosa, which are adjacent to the vagal afferent neurons on which 5-$HT_3$ receptors are located. The released serotonin activates vagal neurons via the 5-$HT_3$ receptors which lead ultimately to a severe emetic response mediated via the chemoreceptor trigger zone within the *area postrema*.

Mechanism of action

Granisetron is a potent anti-emetic and highly selective antagonist of 5-hydroxytryptamine (5-$HT_3$) receptors. Radioligand binding studies have demonstrated that granisetron has negligible affinity for other receptor types including 5-HT and dopamine $D_2$ binding sites.

Chemotherapy- and radiotherapy-induced nausea and vomiting

Granisetron administered orally has been shown to prevent nausea and vomiting associated with cancer chemotherapy in adults.

Post-operative nausea and vomiting

Granisetron administered orally has been shown to be effective for prevention and treatment of post-operative nausea and vomiting in adults.

Pharmacological properties of granisetron

Interaction with neurotropic and other active substances through its activity on P 450-cytochrome has been reported (see section 4.5).

*In vitro* studies have shown that the cytochrome P450 sub-family 3A4 (involved in the metabolism of some of the main narcotic agents) is not modified by granisetron. Although ketaconazole was shown to inhibit the ring oxidation of granisetron *in vitro*, this action is not considered clinically relevant.

Although QT-prolongation has been observed with 5-$HT_3$ receptor antagonists (see section 4.4), this effect is of such occurrence and magnitude that it does not bear clinical significance in normal subjects. Nonetheless it is advisable to monitor both ECG and clinical abnormalities when treating patients concurrently with drugs known to prolong the QT (see section 4.5).

## 5.2 Pharmacokinetic properties

Pharmacokinetics of the oral administration is linear up to 2.5-fold of the recommended dose in adults. It is clear from the extensive dose-finding programme that the antiemetic efficacy is not unequivocally correlated with either administered doses or plasma concentrations of granisetron.

A fourfold increase in the initial prophylactic dose of granisetron made no difference in terms of either the proportion of patient responding to treatment or in the duration of symptoms control.

Absorption

Absorption of granisetron is rapid and complete, though oral bioavailability is reduced to about 60% as a result of first pass metabolism. Oral bioavailability is generally not influenced by food.

Distribution

Granisetron is extensively distributed, with a mean volume of distribution of approximately 3 l/kg. Plasma protein binding is approximately 65%.

Biotransformation

Granisetron is metabolized primarily in the liver by oxidation followed by conjugation. The major compounds are 7-OH-granisetron and its sulphate and glycuronide conjugates. Although antiemetic properties have been observed for 7-OH-granisetron and indazoline N-desmethyl granisetron, it is unlikely that these contribute significantly to the pharmacological activity of granisetron in man. *In vitro* liver microsomal studies show that granisetron's major route of metabolism is inhibited by ketoconazole, suggestive of metabolism mediated by the cytochrome P-450 3A subfamily (see section 4.5).

Elimination

Clearance is predominantly by hepatic metabolism. Urinary excretion of unchanged granisetron averages 12% of dose while that of metabolites amounts to about 47% of dose. The remainder is excreted in faeces as metabolites. Mean plasma half-life in patients by the oral and intravenous route is approximately 9 hours, with a wide inter-subject variability.

Pharmacokinetics in special populations

*Renal failure*

In patients with severe renal failure, data indicate that pharmacokinetic parameters after a single intravenous dose are generally similar to those in normal subjects.

*Hepatic impairment*

In patients with hepatic impairment due to neoplasic liver involvement, total plasma clearance of an intravenous dose was approximately halved compared to patients without hepatic involvement. Despite these changes, no dosage adjustment is necessary (see section 4.2).

*Paediatric population*

These tablets are not recommended in children.

*Elderly patients*

In elderly subjects after single intravenous doses, pharmacokinetic parameters were within the range found for non-elderly subjects.

## 5.3 Preclinical safety data

Preclinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, reproductive toxicity and genotoxicity. Carcinogenicity studies revealed no special hazard for humans when used in the recommended human dose. However, when administered in higher doses and over a prolonged period of time the risk of carcinogenicity cannot be ruled out.

A study in cloned human cardiac ion channels has shown that granisetron has the potential to affect cardiac repolarisation via blockade of HERG potassium channels. Granisetron has been shown to block both sodium and potassium channels, which potentially affects both depolarization and repolarization through prolongation of PR, QRS, and QT intervals. This data helps to clarify the molecular mechanisms by which some of the ECG changes (particularly QT and QRS prolongation) associated with this class of agents occur. However, there is no modification of the cardiac frequency, blood pressure or the ECG trace. If changes do occur, they are generally without clinical significance.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

[To be completed nationally]

### 6.2 Incompatibilities

[To be completed nationally]

### 6.3 Shelf life

[To be completed nationally]

### 6.4 Special precautions for storage

[To be completed nationally]

### 6.5 Nature and contents of container

Blister - [To be completed nationally]

### 6.6 Special precautions for disposal

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

## 7. MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and address}
{tel}
{fax}
{e-mail}

## 8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

## 10. DATE OF REVISION OF THE TEXT

[To be completed nationally]

Detailed information on this medicinal product is available on the website of

## 1. NAME OF THE MEDICINAL PRODUCT

Kytril and associated names (see Annex I) 1 mg/1 ml solution for injection
Kytril and associated names (see Annex I) 3 mg/3 ml solution for injection
Kytril and associated names (see Annex I) 3 mg/1 ml solution for injection
Kytril and associated names (see Annex I) 3 mg/5 ml solution for injection
[See Annex I - To be completed nationally]

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The active substance is granisetron.
Each ml solution for injection contains 1 mg of granisetron (as the hydrochloride).
Each ml solution for injection contains 1 mg of granisetron (as the hydrochloride).
Each ml solution for injection contains 3 mg of granisetron (as the hydrochloride).
Each ml solution for injection contains 0.6 mg of granisetron (as the hydrochloride).

For a full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Solution for injection.
The solution for injection is a clear, colourless liquid.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Kytril solution for injection is indicated in adults for the prevention and treatment of

- acute nausea and vomiting associated with chemotherapy and radiotherapy.
- post-operative nausea and vomiting.

Kytril solution for injection is indicated for the prevention of delayed nausea and vomiting associated with chemotherapy and radiotherapy.

Kytril solution for injection is indicated in children aged 2 years and above for the prevention and treatment of acute nausea and vomiting associated with chemotherapy.

### 4.2 Posology and method of administration

Posology

*Chemo- and radiotherapy-induced nausea and vomiting (CINV and RINV)*

*Prevention (acute and delayed nausea)*

A dose of 1-3 mg (10-40 μg/kg) of Kytril solution for injection should be administered either as a slow intravenous injection or as a diluted intravenous infusion 5 minutes prior to the start of chemotherapy. The solution should be diluted to 5ml per mg.

*Treatment (acute nausea)*

A dose of 1-3 mg (10-40 μg/kg) of Kytril solution for injection should be administered either as a slow intravenous injection or as a diluted intravenous infusion and administered over 5 minutes. The solution should be diluted to 5ml per mg. Further maintenance doses of Kytril solution for injection may be administered at least 10 minutes apart. The maximum dose to be administered over 24 hours should not exceed 9 mg.

*Combination with adrenocortical steroid*

The efficacy of parenteral granisetron may be enhanced by an additional intravenous dose of an adrenocortical steroid e.g. by 8-20 mg dexamethasone administered before the start of the

cytostatic therapy or by 250 mg methyl-prednisolone administered prior to the start and shortly after the end of the chemotherapy.

*Paediatric population*

The safety and efficacy of Kytril solution for injection in children aged 2 years and above has been well established for the prevention and treatment (control) of acute nausea and vomiting associated with chemotherapy and the prevention of delayed nausea and vomiting associated with chemotherapy. A dose of 10-40 µg/kg body weight (up to 3 mg) should be administered as an i.v. infusion, diluted in 10-30 ml infusion fluid and administered over 5 minutes prior to the start of chemotherapy. One additional dose may be administered within a 24 hour-period if required. This additional dose should not be administered until at least 10 minutes after the initial infusion.

*Post-operative nausea and vomiting (PONV)*

A dose of 1 mg (10 µg/kg) of Kytril solution for injection should be administered by slow intravenous injection. The maximum dose of Kytril to be administered over 24 hours should not exceed 3 mg.

For the prevention of PONV, administration should be completed prior to induction of anaesthesia.

*Paediatric population*

Currently available data are described in section 5.1, but no recommendation on a posology can be made. There is insufficient clinical evidence to recommend administration of the solution for injection to children in prevention and treatment of Post-operative nausea and vomiting (PONV).

*Special populations*
*Elderly and renal impairment*

There are no special precautions required for its use in either elderly patients or those patients with renal or hepatic impairment.

*Hepatic impairment*

There is no evidence to date for an increased incidence of adverse events in patients with hepatic disorders. On the basis of its kinetics, whilst no dosage adjustment is necessary, granisetron should be used with a certain amount of caution in this patient group (see section 5.2).

Method of administration

Administration may be as either a slow intravenous injection (over 30 seconds) or as an intravenous infusion diluted in 20 to 50 ml infusion fluid and administered over 5 minutes.

## 4.3 Contraindications

Hypersensitivity to the active substance or any of the excipients.

## 4.4 Special warnings and precautions for use

As granisetron may reduce lower bowel motility, patients with signs of sub-acute intestinal obstruction should be monitored following its administration.

As for other 5-$HT_3$ antagonists, ECG changes including QT interval prolongation have been reported with granisetron. In patients with pre-existing arrhythmias or cardiac conduction disorders this might lead to clinical consequences. Therefore caution should be exercised in patients with cardiac co-morbidities, on cardiotoxic chemotherapy and/or with concomitant electrolyte abnormalities (see section 4.5).

Cross-sensitivity between 5-$HT_3$ antagonists (e.g. dolasetron, ondansetron) has been reported.

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

As for other 5-$HT_3$ antagonists, cases of ECG modifications including QT prolongation have been reported with granisetron. In patients concurrently treated with medicinal products known to

prolong QT interval and/or which are arrhythmogenic, this may lead to clinical consequences (see section 4.4).

In studies in healthy subjects, no evidence of any interaction has been indicated between granisetron and benzodiazepines (lorazepam), neuroleptics (haloperidol) or anti-ulcer medicinal products (cimetidine). Additionally, granisetron has not shown any apparent medicinal product interaction with emetogenic cancer chemotherapies.

No specific interaction studies have been conducted in anaesthetised patients.

### 4.6 Fertility, pregnancy and lactation

Pregnancy

There is limited amount of data from the use of granisetron in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). As a precautionary measure**,** it is preferable to avoid the use of granisetron during pregnancy.

Breastfeeding

It is unknown whether granisetron or its metabolites are excreted in human milk. As a precautionary measure, breast-feeding should not be advised during treatment with Kytril.

Fertility

In rats, granisetron had no harmful effects on reproductive performance or fertility.

### 4.7 Effects on ability to drive and use machines

Kytril is not expected to impair the ability to drive or to use machines.

### 4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse reactions for Kytril are headache and constipation which may be transient. ECG changes including QT prolongation have been reported with Kytril (see sections 4.4 and 4.5).

Tabulated summary of adverse reactions

The following table of listed adverse reactions is derived from clinical trials and post-marketing data associated with Kytril and other 5-$HT_3$ antagonists.

Frequency categories are as follows:
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)

| | |
|---|---|
| ***Immune system disorders*** | |
| *Uncommon* | Hypersensitivity reactions e.g. anaphylaxis, urticaria |
| ***Psychiatric disorders*** | |
| *Common* | Insomnia |
| ***Nervous system disorders*** | |

| | |
|---|---|
| *Very common* | Headache |
| *Uncommon* | Extrapyramidal Reactions |
| ***Cardiac disorders*** | |
| *Uncommon* | QT prolongation |
| ***Gastrointestinal disorders*** | |
| *Very common* | Constipation |
| *Common* | Diarrhoea |
| ***Hepatobiliary disorders*** | |
| *Common* | Elevated hepatic transaminases* |
| ***Skin and subcutaneous tissue disorders*** | |
| *Uncommon* | Rash |

*Occurred at a similar frequency in patients receiving comparator therapy

Description of selected adverse reactions

As for other 5-$HT_3$ antagonists, ECG changes including QT prolongation have been reported with granisetron (see sections 4.4 and 4.5).

### 4.9 Overdose

There is no specific antidote for Kytril. In the case of overdose with the injection, symptomatic treatment should be given. Doses of up to 38.5 mg of Kytril as a single injection have been reported, with symptoms of mild headache but no other reported sequelae.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiemetics and antinauseants, Serotonin (5-$HT_3$) antagonists.
ATC code: A04AA02

Neurological mechanisms, serotonin-mediated nausea and vomiting

Serotonin is the main neurotransmitter responsible for emesis after chemo- or radio-therapy. The 5-$HT_3$ receptors are located in three sites: vagal nerve terminals in the gastrointestinal tract and chemoreceptor trigger zones located in the *area postrema* and the *nucleus tractus solidarius* of the vomiting center in the brainstem. The chemoreceptor trigger zones are located at the caudal end of the fourth ventricle (*area postrema*). This structure lacks an effective blood-brain barrier, and will detect emetic agents in both the systemic circulation and the cerebrospinal fluid. The vomiting centre is located in the brainstem medullary structures. It receives major inputs from the chemoreceptor trigger zones, and a vagal and sympathetic input from the gut.

Following exposure to radiation or catotoxic substances, serotonin (5-HT) is released from enterochromaffine cells in the small intestinal mucosa, which are adjacent to the vagal afferent neurons on which 5-$HT_3$ receptors are located. The released serotonin activates vagal neurons via the 5-$HT_3$ receptors which lead ultimately to a severe emetic response mediated via the chemoreceptor trigger zone within the *area postrema*.

Mechanism of action

Granisetron is a potent anti-emetic and highly selective antagonist of 5-hydroxytryptamine (5-$HT_3$) receptors. Radioligand binding studies have demonstrated that granisetron has negligible affinity for other receptor types including 5-HT and dopamine $D_2$ binding sites.

Chemotherapy- and radiotherapy-induced nausea and vomiting

Granisetron administered intravenously has been shown to prevent nausea and vomiting associated with cancer chemotherapy in adults and children 2 to 16 years of age.

Post-operative nausea and vomiting

Granisetron administered intravenously has been shown to be effective for prevention and treatment of post-operative nausea and vomiting in adults.

Pharmacological properties of granisetron

Interaction with neurotropic and other active substances through its activity on P 450-cytochrome has been reported (see section 4.5).

*In vitro* studies have shown that the cytochrome P450 sub-family 3A4 (involved in the metabolism of some of the main narcotic agents) is not modified by granisetron. Although ketaconazole was shown to inhibit the ring oxidation of granisetron *in vitro*, this action is not considered clinically relevant.

Although QT-prolongation has been observed with 5-$HT_3$ receptors antagonists (see section 4.4), this effect is of such occurrence and magnitude that it does not bear clinical significance in normal subjects. Nonetheless it is advisable to monitor both ECG and clinical abnormalities when treating patients concurrently with drugs known to prolong the QT (see section 4.5).

Paediatric use

Clinical application of granisetron was reported by Candiotti et al. A prospective, multicentre, randomized, double-blind, parallel-group study evaluated 157 children 2 to 16 years of age undergoing elective surgery. Total control of postoperative nausea and vomiting during the first 2 hours after surgery was observed in most patients.

## 5.2 Pharmacokinetic properties

Pharmacokinetics of the oral administration is linear up to 2.5-fold of the recommended dose in adults. It is clear from the extensive dose-finding programme that the antiemetic efficacy is not unequivocally correlated with either administered doses or plasma concentrations of granisetron.

A fourfold increase in the initial prophylactic dose of granisetron made no difference in terms of either the proportion of patient responding to treatment or in the duration of symptoms control.

Distribution

Granisetron is extensively distributed, with a mean volume of distribution of approximately 3 l/kg. Plasma protein binding is approximately 65%.

Biotransformation

Granisetron is metabolized primarily in the liver by oxidation followed by conjugation. The major compounds are 7-OH-granisetron and its sulphate and glycuronide conjugates. Although antiemetic properties have been observed for 7-OH-granisetron and indazoline N-desmethyl granisetron, it is unlikely that these contribute significantly to the pharmacological activity of granisetron in man. *In vitro* liver microsomal studies show that granisetron's major route of metabolism is inhibited by ketoconazole, suggestive of metabolism mediated by the cytochrome P-450 3A subfamily (see section 4.5).

Elimination

Clearance is predominantly by hepatic metabolism. Urinary excretion of unchanged granisetron averages 12% of dose while that of metabolites amounts to about 47% of dose. The remainder is

excreted in faeces as metabolites. Mean plasma half-life in patients by the oral and intravenous route is approximately 9 hours, with a wide inter-subject variability.

Pharmacokinetics in special populations

*Renal failure*

In patients with severe renal failure, data indicate that pharmacokinetic parameters after a single intravenous dose are generally similar to those in normal subjects.

*Hepatic impairment*

In patients with hepatic impairment due to neoplasic liver involvement, total plasma clearance of an intravenous dose was approximately halved compared to patients without hepatic involvement. Despite these changes, no dosage adjustment is necessary (see section 4.2).

*Elderly patients*

In elderly subjects after single intravenous doses, pharmacokinetic parameters were within the range found for non-elderly subjects.

*Paediatrics*

In children, after single intravenous doses, pharmacokinetics are similar to those in adults when appropriate parameters (volume of distribution, total plasma clearance) are normalized for body weight.

### 5.3 Preclinical safety data

Preclinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, reproductive toxicity and genotoxicity. Carcinogenicity studies revealed no special hazard for humans when used in the recommended human dose. However, when administered in higher doses and over a prolonged period of time the risk of carcinogenicity cannot be ruled out.
A study in cloned human cardiac ion channels has shown that granisetron has the potential to affect cardiac repolarisation via blockade of HERG potassium channels. Granisetron has been shown to block both sodium and potassium channels, which potentially affects both depolarization and repolarization through prolongation of PR, QRS, and QT intervals. This data helps to clarify the molecular mechanisms by which some of the ECG changes (particularly QT and QRS prolongation) associated with this class of agents occur. However, there is no modification of the cardiac frequency, blood pressure or the ECG trace. If changes do occur, they are generally without clinical significance.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

[To be completed nationally]

### 6.2 Incompatibilities

[To be completed nationally]

### 6.3 Shelf life

[To be completed nationally]

### 6.4 Special precautions for storage

Do not store above 30ºC.
Keep container in the outer carton in order to protect from light.

### 6.5 Nature and contents of container

The solution for injection is primary packed in standard colourless glass ampoules with 1 ml 3 ml nominal volume
[To be completed nationally]

### 6.6 Special precautions for disposal

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

## 7. MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and address}
{tel}
{fax}
{e-mail}

## 8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

## 10. DATE OF REVISION OF THE TEXT

[To be completed nationally]

Detailed information on this medicinal product is available on the website of the

# LABELLING

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON**

**1. NAME OF THE MEDICINAL PRODUCT**

Kytril and associated names (see Annex I) 1 mg film-coated tablets
Kytril and associated names (see Annex I) 2 mg film-coated tablets
[See Annex I - To be completed nationally]

Granisetron

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each film-coated tablet contains 1 mg granisetron (as hydrochloride).
Each film-coated tablet contains 2 mg granisetron (as hydrochloride).

**3. LIST OF EXCIPIENTS**

Lactose monohydrate
See the leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Film-coated tablet.
[To be completed nationally]

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.
Oral use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

Keep out of the reach and sight of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

[To be completed nationally]

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

[See Annex I - To be completed nationally]

{Name and address}
{tel}
{fax}
{e-mail}

## 12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

## 13. BATCH NUMBER

Batch

## 14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

[To be completed nationally]

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON**

## 1. NAME OF THE MEDICINAL PRODUCT

Kytril and associated names (see Annex I) 1 mg/1 ml solution for injection
Kytril and associated names (see Annex I) 3 mg/3 ml solution for injection
Kytril and associated names (see Annex I) 3 mg/1 ml solution for injection
Kytril and associated names (see Annex I) 3 mg/5 ml solution for injection
[See Annex I - To be completed nationally]

Granisetron

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml solution for injection contains 1 mg granisetron (as hydrochloride).
Each ml solution for injection contains 1 mg granisetron (as hydrochloride).
Each ml solution for injection contains 3 mg granisetron (as hydrochloride).
Each ml solution for injection contains 0.6 mg granisetron (as hydrochloride).

## 3. LIST OF EXCIPIENTS

[To be completed nationally]

## 4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection.
[To be completed nationally]

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intravenous use.

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Do not store above 30ºC.
Keep container in the outer carton. in order to protect from light.

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and address}
{tel}
{fax}
{e-mail}

## 12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

## 13. BATCH NUMBER

Batch

## 14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

## 15. INSTRUCTIONS ON USE

[To be completed nationally]

## 16. INFORMATION IN BRAILLE

[To be completed nationally]

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**BLISTERS**

**1. NAME OF THE MEDICINAL PRODUCT**

Kytril and associated names (see Annex I) 1 mg film-coated tablets
Kytril and associated names (see Annex I) 2 mg film-coated tablets
[See Annex I - To be completed nationally]

Granisetron

**2. NAME OF THE MARKETING AUTHORISATION HOLDER**

[See Annex I - To be completed nationally]

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. OTHER**

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**AMPOULES**

## 1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Kytril and associated names (see Annex I) 1 mg/1 ml solution for injection
Kytril and associated names (see Annex I) 3 mg/3 ml solution for injection
Kytril and associated names (see Annex I) 3 mg/1 ml solution for injection
Kytril and associated names (see Annex I) 3 mg/5 ml solution for injection
[See Annex I - To be completed nationally]

Granisetron
Intravenous use

## 2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Batch

## 5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

[To be completed nationally]

## 6. OTHER

# PACKAGE LEAFLET

**PACKAGE LEAFLET: INFORMATION FOR THE USER**

Kytril and associated names (see Annex I) 1 mg film-coated tablets
Kytril and associated names (see Annex I) 2 mg film-coated tablets
[See Annex I - To be completed nationally]

Granisetron

**Read all of this leaflet carefully before you start taking this medicine.**
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, nurse or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor, nurse or pharmacist.

**In this leaflet**:


## 1. WHAT KYTRIL IS AND WHAT IT IS USED FOR

Kytril contains a medicine called granisetron. This belongs to a group of medicines called '5-$HT_3$ receptor antagonists' or 'anti-emetics'. These tablets are only for use in adults.

Kytril is used to prevent or treat nausea and vomiting (feeling and being sick) caused by other medical treatments, such as chemotherapy or radiotherapy for cancer.

## 2. BEFORE YOU TAKE KYTRIL

### Do not take Kytril tablets

- if you are allergic (hypersensitive) to granisetron or any of the other ingredients of Kytril (listed in section 6: Further information and "Important Information about some of the ingredients Kytril below".

If you are not sure, talk to your doctor, nurse or pharmacist before taking these tablets.

### Take special care with Kytril

Check with your doctor, nurse or pharmacist before using these tablets, if you:
- are having problems with your bowel movements because of a blockage of your gut (intestines)
- have heart problems, are being treated for cancer with a medicine that is known to damage your heart or have problems with levels of salts, such as potassium, sodium or calcium, in your body (electrolyte abnormalities)
- are taking other '5-$HT_3$ receptor antagonist' medicines. These include dolasetron, ondansetron used like Kytril in the treatment and prevention of nausea and vomiting.

### Children

Children should not take these tablets.

### Taking other medicines

Please tell your doctor, nurse or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. This is because Kytril can affect the way some medicines work. Also some other medicines can affect the way these tablets work.

In particular, tell your doctor, nurse or pharmacist if you are taking the following medicines:
- medicines used to treat an irregular heartbeat, other '5-$HT_3$ receptor antagonist' medicines such as dolasetron or ondansetron (see "Take special care with Kytril" above)
- phenobarbital, a medicine used to treat epilepsy
- a medicine called ketoconazole used in the treatment of fungal infections
- the antibiotic erythromycin used to treat bacterial infections.

**Pregnancy and breast-feeding**

You should not take these tablets if you are pregnant, trying to get pregnant or are breast-feeding, unless your doctor has told you to.

Ask your doctor, nurse or pharmacist for advice before taking any medicine.

**Driving and using machines**

Kytril has no or negligible affect on your ability to drive or use any tools or machines.

**Important information about some of the ingredients of Kytril**

This medicine contains lactose (a type of sugar). If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

## 3. HOW TO TAKE KYTRIL

Always take Kytril exactly as your doctor has told you. You should check with your doctor, nurse or pharmacist if you are not sure.

The dose of Kytril varies from one patient to another. It depends on your age, weight, and whether you are being given the medicine to prevent, or treat, nausea and vomiting. The doctor will work out how much to give you.

**Prevention of feeling or being sick**

Your first dose of Kytril will usually be given an hour before your radio- or chemotherapy. The dose will be either one or two 1 mg tablets or one 2 mg tablet once a day for up to a week after your radio- or chemotherapy.

**Treatment of feeling or being sick**

The dose will usually be either one or two 1 mg tablets or one 2 mg tablet once a day, but your doctor may decide to increase your dose to upto nine 1 mg tablets a day.

**If you take more Kytril than you should**

If you think you have taken too many of the tablets talk to your doctor or nurse. The symptoms of overdose include mild headaches. You will be treated depending on your symptoms.

**If you forget to take Kytril**

If you think you have forgotten to take your medicine speak to your doctor or nurse.

Do not take a double dose to make up for a forgotten tablet.

**If you stop taking Kytril**

Do not stop taking your medicine before the treatment is finished. If you do stop taking your medicine, your symptoms may return.

If you have any further questions on the use of this medicine, ask your doctor, nurse or pharmacist.

## 4. POSSIBLE SIDE EFFECTS

Like all medicines, Kytril can cause side effects, although not everybody gets them. If you notice the following problem you must see a doctor straight away:

- allergic reactions (anaphylaxis). The signs may include swelling of the throat, face, lips and mouth, difficultly in breathing or swallowing.

Other side effects that may be experienced while taking this medicine are:
Very common: affects more than 1 user in 10

- headache
- constipation. Your doctor will monitor your condition.

Common: affects 1 to 10 users in 100

- problems sleeping (insomnia)
- changes in how your liver is working shown by blood tests
- diarrhoea.

Uncommon: affects 1 to 10 users in 1,000

- skin rashes or an allergic skin reaction or "nettle-rash" or "hives" (urticaria). The signs may include red, raised itchy bumps
- changes in the heartbeat (rhythm) and changes seen on ECG readings (electrical recordings of the heart)
- abnormal involuntary movements, such as shaking, muscle rigidity and muscle contractions.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor, nurse or pharmacist.

## 5. HOW TO STORE KYTRIL

Keep out of the reach and sight of children.

The tablets should not be used after the expiry date which is stated on the {container [TO be completed nationally] } and carton after EXP. The expiry date refers to the last day of that month.

[To be completed nationally]

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

## 6. FURTHER INFORMATION

### What Kytril contains

The active substance is granisetron.
Each film-coated tablet contains 1 mg granisetron (as the hydrochloride).
Each film-coated tablet contains 2 mg granisetron (as the hydrochloride).

The other ingredients are:

[To be completed nationally]

### What Kytril looks like and contents of the pack

Blisters - [To be completed nationally]

### Marketing Authorisation Holder and Manufacturer

[See Annex I - To be completed nationally]

{Name and address}
{tel}

{fax}
{e-mail}

**This medicinal product is authorised in the Member States of the EEA under the following names:**

Austria, Belgium, Bulgaria, Czech Republic, Estonia, Finland, France, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Portugal, Romania, Slovak Republic, Slovenia, Spain, Sweden and United Kingdom: Kytril

Germany: Kevatril

**This leaflet was last approved in** {MM/YYYY}.

[To be completed nationally]

Detailed information on this product is available on the website of

**PACKAGE LEAFLET: INFORMATION FOR THE USER**

Kytril and associated names (see Annex I) 1 mg/1 ml solution for injection
Kytril and associated names (see Annex I) 3 mg/3 ml solution for injection
Kytril and associated names (see Annex I) 3 mg/1 ml solution for injection
Kytril and associated names (see Annex I) 3 mg/5 ml solution for injection
[See Annex I - To be completed nationally]

Granisetron

**Read all of this leaflet carefully before you start taking this medicine.**
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, nurse or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor, nurse or pharmacist.

**In this leaflet**:


## 1. WHAT KYTRIL IS AND WHAT IT IS USED FOR

Kytril contains a medicine called granisetron. This belongs to a group of medicines called '5-$HT_3$ receptor antagonists' or 'anti-emetics'.

Kytril is used to prevent or treat nausea and vomiting (feeling and being sick) caused by other medical treatments, such as chemotherapy or radiotherapy for cancer, and by surgery.

The solution for injection is for use in adults and children from 2 years old.

## 2. BEFORE YOU ARE GIVEN KYTRIL

### Do not use Kytril

- if you are allergic (hypersensitive) to granisetron or any of the other ingredients of Kytril (listed in Section 6: Further information).

If you are not sure, talk to your doctor, nurse or pharmacist before having the injection.

### Take special care with Kytril

Check with your doctor, nurse or pharmacist before using Kytril if you:
- are having problems with your bowel movements because of a blockage of your gut (intestines)
- have heart problems, are being treated for cancer with a medicine that is known to damage your heart or have problems with levels of salts, such as potassium, sodium or calcium, in your body (electrolyte abnormalities)
- are taking other '5-$HT_3$ receptor antagonist' medicines. These include dolasetron, ondansetron used like Kytril in the treatment and prevention of nausea and vomiting.

### Taking other medicines

Please tell your doctor, nurse or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. This is because Kytril can affect the way some medicines work. Also some other medicines can affect the way this injection works.

In particular, tell your doctor, nurse or pharmacist if you are taking the following medicines:

- medicines used to treat an irregular heartbeat other '5-$HT_3$ receptor antagonist' medicines such as dolasetron or ondansetron (see "Take special care with Kytril" above)
- phenobarbital, a medicine used to treat epilepsy
- a medicine called ketoconazole used in the treatment of fungal infections
- the antibiotic erythromycin used to treat bacterial infections.

**Pregnancy and breast-feeding**

You should not have this injection if you are pregnant, trying to get pregnant or are breast-feeding, unless your doctor has told you to.

Ask your doctor, nurse or pharmacist for advice before taking any medicine.

**Driving and using machines**

Kytril is not likely to affect your ability to drive or use any tools or machines.

## 3. HOW KYTRIL WILL BE GIVEN

The injection will be given to you by a doctor or nurse. The dose of Kytril varies from one patient to another. It depends on your age, weight, and whether you are being given the medicine to prevent, or treat, nausea and vomiting. The doctor will work out how much to give you.

Kytril can be given as an injection into the veins (intravenous).

**Prevention of feeling or being sick following radio- or chemotherapy**

You will be given the injection before your radio- or chemotherapy starts. The injection into your veins will take between 30 seconds and 5 minutes and the dose will usually be between 1 and 3 mg. The medicine may be diluted before it is injected.

**Treatment of feeling or being sick following radio- or chemotherapy**

The injection will take between 30 seconds and 5 minutes and the dose will usually be between 1 and 3 mg. The medicine may be diluted before it is injected into your veins. You may be given more injections to stop your sickness after the first dose. There will be at least 10 minutes between each injection. The most Kytril you will be given is 9 mg a day.

**Combination with steroids**

The effect of the injection may be improved by the use of medicines called adrenocortical steroids. The steroid will be given either as a dose between 8 and 20 mg dexamethasone before your radio- or chemotherapy or as 250 mg methyl-prednisolone, which will be given both before and after your radio- or chemotherapy.

**Use in children in the prevention or treatment of feeling or being sick following radio- or chemotherapy**

Children will be given Kytril by injections into the vein as described above with the dose depending on the child's weight. The injections will be diluted and be given before radio- or chemotherapy and will take 5 minutes. Children will be given a maximum of 2 doses a day, at least 10 minutes apart.

**Treatment of feeling or being sick following surgery**

The injection into your veins will take between 30 seconds and 5 minutes and the dose will usually be 1 mg. The most Kytril you will be given is 3 mg a day.

**Use in children in the prevention or treatment of feeling or being sick following surgery**

Children should not be given this injection to treat sickness or the feeling of sickness after surgery.

**If you are given too much Kytril**

Because the injection will be given to you by a doctor or nurse, it is unlikely that you will be given too much. However, if you are worried talk to your doctor or nurse. Symptoms of overdose include mild headaches. You will be treated depending on your symptoms.

If you have any further questions on the use of this medicine, ask your doctor, nurse or pharmacist.

## 4. POSSIBLE SIDE EFFECTS

Like all medicines, Kytril can cause side effects, although not everybody gets them. If you notice the following problem you must see a doctor straight away:

- allergic reactions (anaphylaxis). The signs may include swelling of the throat, face, lips and mouth, difficultly in breathing or swallowing.

Other side effects that may be experienced while taking this medicine are:

Very common: affects more than 1 user in 10
- headache
- constipation. Your doctor will monitor your condition.

Common: affects 1 to 10 users in 100
- problems sleeping (insomnia)
- changes in how your liver is working shown by blood tests
- diarrhoea.

Uncommon: affects up to 1 to 10 users in 1,000
- skin rashes or an allergic skin reaction or "nettle-rash" or "hives" (urticaria). The signs may include red, raised itchy bumps
- changes in the heartbeat (rhythm) and changes seen on ECG readings (electrical recordings of the heart)
- abnormal involuntary movements, such as shaking, muscle rigidity and muscle contractions.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor, nurse or pharmacist.

## 5. HOW TO STORE KYTRIL

[To be completed nationally]

Keep out of the reach and sight of children.

The solution for injection should not be use after the expiry date which is stated on the carton and/or ampoule after EXP. The expiry date refers to the last day of that month.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

## 6. FURTHER INFORMATION

**What Kytril contains**

The active substance is granisetron.
Each ml solution for injection contains 1 mg of granisetron (as hydrochloride).
Each ml solution for injection contains 1 mg of granisetron (as hydrochloride).
Each ml solution for injection contains 3 mg of granisetron (as hydrochloride).
Each ml solution for injection contains 0.6 mg of granisetron (as hydrochloride).

The other ingredients are sodium chloride, water for injections, citric acid monohydrate, hydrochloric acid and sodium hydroxide for pH (acidity) adjustment.

[To be completed nationally]

**What Kytril looks like and contents of the pack**

Ampoules - [To be completed nationally]

**Marketing Authorisation Holder and Manufacturer**

[To be completed nationally]

**This medicinal product is authorised in the Member States of the EEA under the following names:**

Austria, Belgium, Bulgaria, Czech Republic, Estonia, Finland, France, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Portugal, Romania, Slovak Republic, Slovenia, Spain, Sweden and United Kingdom: Kytril

Germany: Kevatril

**This leaflet was last approved in** {MM/YYYY}.

[To be completed nationally]

Detailed information on this product is available on the website of