Safeguarding public health

MHRA

Public Assessment Report

Decentralised Procedure

GRANISETRON 1MG/ML CONCENTRATE FOR SOLUTION FOR INJECTION/INFUSION

UK/H/1439/001/DC
UK licence no: PL 08828/0191

Fresenius Kabi Limited

GRANISETRON 1MG/ML CONCENTRATE FOR SOLUTION FOR INJECTION/INFUSION

LAY SUMMARY

On 21st November 2008, Austria, Belgium, Czech Republic, Germany, Greece, Spain, Finland, Hungary, Italy, Luxembourg, The Netherlands, Portugal, Romania, Sweden, the Slovak Republic and the UK agreed to grant marketing authorisations to Fresenius Kabi Limited for the medicinal product Granisetron 1mg/ml Concentrate for Solution for Injection/Infusion. The licence was granted via the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS). After the national phase, a licence was granted in the UK on 22nd January 2009.

Granisetron 1mg/ml Concentrate for Solution for Injection/Infusion is used to prevent or treat nausea (feeling sick) or vomiting (being sick).

The active ingredient granisetron hydrochloride, belongs to a group of medicines called 5-HT3 receptor antagonists. These act as anti-emetics.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Granisetron 1mg/ml Concentrate for Solution for Injection/Infusion outweigh the risks, hence a Marketing Authorisation has been granted.

TABLE OF CONTENTS

Module 1

Product Name	Granisetron 1mg/ml Concentrate for Solution for Injection/Infusion
Type of Application	Generic application, Article 10.1
Active Substance	Granisetron hydrochloride
Form	Concentrate for solution for infusion
Strength	1mg/ml concentrate for solution for infusion
MA Holder	Fresenius Kabi Limited, Cestrian Court, Eastgate Way, Manor Park, Runcorn, Cheshire, WA7 1NT, UK
RMS	UK
CMS	Austria, Belgium, Czech Republic, Germany, Greece, Spain, Finland, Hungary, Italy, Luxembourg, The Netherlands, Portugal, Romania, Sweden, the Slovak Republic and the UK
Procedure Number	UK/H/1439/001/DC
Timetable	Day 210 – 21st November 2008

Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Granisetron 1mg/ml concentrate for solution for injection/infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml contains granisetron hydrochloride equivalent to 1 mg granisetron.
3 ml contains granisetron hydrochloride equivalent to 3 mg granisetron.

Excipients: 3.5 mg of sodium per ml.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for injection/infusion
Clear colourless solution at pH 5.0-5.7

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Granisetron is indicated for the prevention or treatment of nausea and vomiting induced by cytostatic therapy (chemotherapy and radiotherapy) in adults, and children and adolescents aged 2 years and older.

4.2 Posology and method of administration

Granisetron 1mg/1ml is for intravenous administration only
For instructions for dilution see section 6.6

Adults
The dose can be administered as an intravenous bolus over not less than 30 seconds diluted with compatible infusion fluid. The contents of a 1 ml ampoule should be diluted to a volume of 5 ml; the contents of a 3 ml ampoule should be diluted to a volume of 15 ml.

Granisetron can also be diluted in 20 to 50 ml infusion fluid and then administered over 5 minutes.

Prevention:
The recommended dose of Granisetron is 1 mg or 3 mg depending on the emetogenic potential of the chemotherapy or radiotherapy. In clinical trials, the majority of patients have required only a single dose of granisetron to control nausea and vomiting over 24 hours.

There is clinical experience in patients receiving daily administration for up to five consecutive days in one course of therapy.

It is recommended to administer the dose not more than 30 minutes before the start of cytostatic therapy. Prophylactic administration of Granisetron should be completed prior to the start of cytostatic therapy.

Treatment:
The same dose of Granisetron should be used for treatment as prevention. Additional doses should be administered at least 10 minutes apart.

Maximum daily dosage:
Up to three doses of 3mg Granisetron may be administered within a 24-hour period. The maximum dose of Granisetron to be administered over 24 hours should not exceed 9 mg.

Concomitant use of corticosteroids
The efficacy of Granisetron may be enhanced by addition of dexamethasone (8 – 20 mg) or methylprednisolone (250 mg).

Children 2 years of age and older
Prevention:
A single dose of 20 – 40 µg granisetron/kg body weight (up to 3 mg) should be administered as an intravenous infusion, diluted in 10 to 30 ml of infusion fluid (see section 6.6) and administered over five minutes. Administration should be completed prior to the start of cytostatic therapy.

Treatment:
The same dose of granisetron as above should be used for treatment as prevention.

One additional dose of 20-40µg granisetron/kg body weight (up to 3mg) may be administered within a 24 hour period either as a single dose or as two divided doses. This additional dose should be administered at least 10 minutes apart from the initial infusion.

There are no sufficient data in children under 2 years of age. Therefore Granisetron should not be used in children below 2 years of age.

Elderly Patients
No special requirements apply

Renal impairment
No special requirements apply

Hepatic impairment
No special requirements apply

4.3 Contraindications
Hypersensitivity to the active substance or to any of the excipients of Granisetron (see section 6.1)

4.4 Special warnings and precautions for use
Granisetron may reduce intestinal motility. Patients showing symptoms of sub-acute intestinal obstruction following administration of Granisetron should be monitored carefully.

5-HT3 antagonists, such as granisetron, may be associated with arrhythmias or ECG abnormalities. This potentially may have clinical significance in patients with pre-existing arrhythmias or cardiac conduction disorders or patients who are being treated with antiarrhythmic agents or beta-blockers.

No special precautions are required for the elderly or renally and/or hepatically impaired patient. Although to date no signs of an increased incidence of adverse events have been observed in hepatically impaired patients, owing to the kinetics a degree of caution should be exercised in using granisetron with this category.

This medicinal product contains 1.37 mmol sodium (or 31.5 mg) per maximum daily dose of 9 mg. To be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction
No definitive drug-drug interaction study has been performed. Granisetron is primarily metabolised by CYP3A enzymes and does not induce or inhibit any other CYP enzymes.

In vitro, it could be shown that metabolism of granisetron is inhibited by ketoconazole, a potent CYP3A inhibitor. Coadministration of granisetron with systemic ketoconazole may, therefore, increase granisetron's elimination half-life.

In humans, hepatic enzyme induction with phenobarbital resulted in an increase in total plasma clearance of granisetron of approximately 25 %. The clinical significance of this change is not known.

So far no signs of interaction have been observed between granisetron and medicinal products that are often prescribed in anti-emetic therapy, such as benzodiazepines, neuroleptics and anti-ulcer medications.

Granisetron injections have shown no apparent drug interaction with emetogenic cancer chemotherapies.

No specific interaction studies have been conducted in anaesthetised patients, but granisetron injections have been safely administered with commonly used anaesthetic and analgesic agents.

4.6 Pregnancy and lactation

Pregnancy

Whilst animal studies have shown no teratogenic effects, there is no experience with the use of granisetron during human pregnancy. Therefore Granisetron should not be administered to women who are pregnant unless there are compelling clinical reasons.

Lactation

There are no data on the excretion of granisetron in breast milk. Breast feeding should therefore be discontinued during therapy with Granisetron

4.7 Effects on ability to drive and use machines

Somnolence is a common side effect observed after granisetron treatment. Depending on the patient's individual reaction this may impair his/her ability to drive, to operate machinery or to work at high altitude. If the patient feels drowsy after treatment with Granisetron he/she should be advised not to drive, not to operate machinery and not to carry out any work that requires safe foothold.

4.8 Undesirable effects

The most frequent adverse effect is headache, occurring in about 14% of patients. Other less common adverse events associated with granisetron administration include hypersensitivity reactions (e.g. anaphylaxis), constipation, diarrhoea, asthenia and somnolence.

The frequency of side effects is classified into the following categories:

Very common	≥1/10
Common	≥1/100, <1/10
Uncommon	≥1/1.000, <1/100
Rare	≥1/10.000, <1/1.000
Very rare	<1/10.000, not known (cannot be estimated from the available data)

Incidence and severity are given in the following table:

Cardiac disorders	Rare: arrhythmias such as sinus bradycardia, atrial fibrillation, varying degrees of AV-block, ventricular ectopy (including non-sustained tachycardia), ECG abnormalities
Nervous system disorders	Very common: headache Common: somnolence, agitation, anxiety, insomnia, taste disorder Rare: dystonia and dyskinesia have been reported with medicines in the 5-HT3 antagonist class
Eye disorders	Uncommon: abnormal vision
Ear and labyrinth disorders	Common: dizziness
Gastrointestinal disorders	Common: diarrhoea, constipation, anorexia
Skin and subcutaneous tissue disorders	Uncommon: skin rashes Rare: local irritations at administration site after repeated intravenous administration
Vascular disorders	Common: hypertension Rare: hypotension
General disorders	Common: fever, asthenia
Immune system disorders	Rare: hypersensitivity reactions, sometimes severe (e.g., anaphylaxis, shortness of breath, hypotension, urticaria) Very rare: oedema (including facial oedema)
Hepatobiliary disorders	Rare: abnormal hepatic function, raised transaminase levels

4.9 Overdose

Overdosage of up to 30 mg of granisetron injection (10 times the recommended dose) has been reported without symptoms or only the occurrence of a slight headache. There is no specific antidote for granisetron overdosage. In case of overdosage, symptomatic treatment should be given.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group (ATC code): Serotonin (5-HT3) antagonists (A04AA02)
Granisetron is a potent anti-emetic and highly selective antagonist of 5-hydroxytryptamine (5-HT3) receptors. Radioligand binding studies have demonstrated that granisetron has negligible affinity for other receptor types, including 5-HT and dopamine D2 binding sites.

Granisetron is effective intravenously, either prophylactically or by intervention, in abolishing the retching and vomiting evoked by administration of cytotoxic drugs or by whole body X-irradiation.

5.2 Pharmacokinetic properties

General characteristics

Absorption

Following intravenous doses in the range of 20-160 µg/kg, plasma pharmacokinetics (Cmax and AUC) were generally dose-proportional in both healthy subjects and in patients receiving chemotherapy. The mean plasma half-life was 5.2 h in healthy subjects and 8.7 h in patients receiving chemotherapy.

Distribution

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

Biotransformation

Biotransformation pathways involve N-demethylation and aromatic ring oxidation followed by conjugation.

Elimination

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

Characteristics in patients

The plasma concentration of granisetron is not clearly correlated with the anti-emetic efficacy. Clinical benefit may be conferred even when granisetron is not detectable in plasma.

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

In children, after a single IV dose, the pharmacokinetics resembles that of adults when relevant parameters (volume of distribution, plasma clearance) are adjusted for body weight.

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

In patients with hepatic impairment due to neoplastic 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.

5.3 Preclinical safety data

Preclinical data revealed no special hazard for humans based on conventional studies of repeated-dose toxicity, carcinogenicity, reproductive toxicity and genotoxicity.

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid, monohydrate
Hydrochloric acid (for pH adjustment)
Sodium chloride
Sodium hydroxide (for pH adjustment)
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Shelf life of the finished medicinal product:
2 years

After first opening:
Once opened the product should be used immediately.

After dilution:
Chemical and physical in-use stability has been demonstrated for 24 hours at 25 ºC protected from direct sunlight.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions

6.4 Special precautions for storage

Keep the ampoules in the outer carton in order to protect from light. Do not freeze.

For storage conditions of the diluted medicinal product, see section 6.3.

6.5 Nature and contents of container

3 ml, type I clear glass ampoules
1 ml, type I clear glass ampoules

Pack sizes:
5 x 1 ml, 10 x 1 ml
5 x 3 ml, 10 x 3 ml

6.6 Special precautions for disposal

Dilute before use. For single use only. Any unused portion should be discarded.
The diluted injections and infusions are to be inspected visually for particulate matter prior to administration. They should only be used if the solution is clear and free from particles.

Preparing the infusion

Adults: The contents of a 1 ml ampoule can be diluted to a volume of 5 ml; the contents of a 3 ml ampoule can be diluted to a volume of 15 ml.

Granisetron can also be diluted in 20 to 50 ml compatible infusion fluid and then given over five minutes as an intravenous infusion in any of the following solutions:

0.9 % w/v sodium chloride injection
5 % w/v glucose injection
Lactated Ringer's Solution;

No other diluents should be used.

Children 2 years of age and older: To prepare the dose of 20 - 40 µg/kg, the appropriate volume is withdrawn and diluted with infusion fluid (as for adults) to a total volume of 10 to 30 ml.

As a general precaution, Granisetron should not be mixed in solution with other drugs.

Granisetron 1 mg / ml is compatible with Dexamethason dihydrogenphosphate dinatrium in a concentration of 10-60 µg/ml of Granisetron and 80-480 µg/ml Dexamethasonphosphate diluted in sodium chloride 0.9 % or Glucose 5 % solution over a period of 24 hours.

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

7 MARKETING AUTHORISATION HOLDER

Fresenius Kabi Limited
Cestrian Court
Eastgate Way
Manor Park
Runcorn
Cheshire
WA7 1NT
UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 08828/0191

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

22/01/2009

10 DATE OF REVISION OF THE TEXT

22/01/2009

Module 3

Package Leaflet: Information for the user

Granisetron 1 mg / ml concentrate for solution for injection/infusion (Granisetron)

Read all of this leaflet carefully before you start using this medicine.
Keep this leaflet. You may need to read it again.
If you have any further questions, ask your doctor 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 get 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 Granisetron is and what it is used for

Granisetron contains an ingredient called granisetron.
This belongs to a group of medicines called 5-HT3 receptor antagonists which act as anti-emetics. It is used to prevent or treat nausea (feeling sick) or vomiting (being sick).

Granisetron is given to adults or children aged 2 years and older to prevent or treat some side effects caused by certain types of treatment such as cancer chemotherapy or radiotherapy.

2. Before you are given Granisetron

Do not use Granisetron:
- If you are allergic (hypersensitive) to granisetron or any of the other ingredients of this medicine (see **Section 6**)
- in children under 2 years of age because insufficient experience is available.

Do not have Granisetron if the above applies to you. If you are not sure talk to your doctor, nurse or pharmacist before having Granisetron.

Take special care with Granisetron
Check with your doctor, nurse or pharmacist if:
- you have any problems with your bowel such as sub-acute intestinal blockage. This is because Granisetron may slow down the speed that food is carried through to your lower bowel
- you have heart rhythm disorders

If you are not sure if the above applies to you, talk to your doctor, nurse or pharmacist before having Granisetron.
Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Having Granisetron with food and drink
You can eat and drink as usual when having Granisetron.
You do not need to change your diet unless suggested by your doctor.

Pregnancy and breast feeding
Tell your doctor, nurse of pharmacist if:
- you are pregnant, might become pregnant or think you might be pregnant
- you are breast-feeding or planning to breast-feed.

In the above cases, Granisetron should only be given if absolutely necessary for medical reasons.

Ask your doctor or pharmacist for advice before taking any medicine, if you are pregnant or breast-feeding.

Driving and using machines
After being treated with Granisetron there is a chance that you feel drowsy or sleepy. Depending on your individual reaction this may compromise your ability to drive, to operate machinery or to work at high altitude. If that happens you should not drive by yourself in public traffic, not operate machinery and not carry out any work that requires a safe foothold until you're aware of how this drug affects you.

Important information about some of the ingredients of Granisetron
Sodium: Granisetron contains 31.5 mg (1.37 mmol) of sodium per maximum daily dose of 9 mg To be taken into consideration by patients on a controlled sodium diet.

3. How Granisetron is given

Granisetron is a medicine used in hospitals. It will be given to you by a doctor or nurse:
- In adults, it is given as a slow intravenous injection (in to a vein) over at least 30 seconds or as a continuous infusion (drip into a vein) over a period of 5 minutes.
- In children, it is given as a continuous infusion (drip into a vein) over a period of 5 minutes.

Granisetron, is usually given before the treatment that may make you feel sick. It can also be given after other treatments to stop any sickness that you may have.

(For further instructions see: "The following information is intended for medical or healthcare professionals only" at the end of this package leaflet).

How much Granisetron is given
Your doctor will decide on the dose.
The usual dosage in prevention or treatment of nausea and vomiting is:

Adults
- 1 or 3 milligrams (mg)
- The same dose may be given to you for up to two more times within 24 hours, if needed.
- The maximum daily dose should not exceed 9 mg.

Children (2 years of age and older)
- The dose depends on the child's weight.
- The usual dose is 20-40 micrograms for each kg of body weight as a single dose (up to a maximum of 3 mg)
- One additional dose of 20-40 micrograms / kg (up to a maximum of 3 mg) may be given in a 24-hour period either as a single dose or as two divided doses.

If you have more Granisetron than you should
If you think you have been given too much of this medicine, tell your doctor, nurse or pharmacist straight away.

If you forget to use Granisetron
If you think you have missed an injection, speak to your doctor, nurse or pharmacist.

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

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4. Possible side effects

Like all medicines Granisetron can cause side effects, although not everybody gets them. The most frequent side effect is headache.

You should tell your doctor **immediately** if you become short of breath or get a swollen face. These reactions are rare but need urgent medical treatment.
Tell your doctor as well if you get a rash or start to itch.

The following side effects may occur during treatment with Granisetron:

Very common side effects (probably affecting more than 1 in 10 people):

- Headache

Common side effects (probably affecting fewer than 1 in 10 people):

- High blood pressure (hypertension)
- Feeling anxious (anxiety)
- Restlessness (agitation)
- Sleeplessness (insomnia)
- Drowsiness (somnolence)
- Giddiness (dizziness)
- Weakness (asthenia)
- Diarrhoea
- Constipation
- Loss of appetite (anorexia)
- Taste disorder
- Fever

Uncommon side effects (probably affecting fewer than 1 in 100 people):

- Disturbances of vision (abnormal vision)
- Skin rashes

Rare side effects (probably affecting fewer than 1 in 1,000 people):
- Irregular rhythm of the heartbeat (arrhythmias: sinus bradycardia, atrial fibrillation, varying degrees of AV-block, ventricular ectopy)
- Abnormalities in the ECG (prolonged ECG intervals)
- Muscle coordination problems like twisting , repetitive movements, or abnormal postures (dystonia)
- Involuntary movement (dyskinesia)
- Low blood pressure (hypotension)
- Hypersensitivity reactions, sometimes severe (e.g. anaphylaxis, shortness of breath, low blood pressure, hives)
- Allergic reactions (including slight rash)
- Local inflammation at the site of injection after repeated application

Very rare side effects (probably affecting fewer than 1 in 10,000 people):

- Swellings, including swellings of the face (oedema)

If you are having blood tests, tell your doctor you have been given Granisetron because it sometimes causes changes in tests of liver function.

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 Granisetron

Keep out of the reach and sight of children
- Do not use Granisetron after the expiry date which is stated on the pack. The expiry date refers to the last day of that month
- Keep in the outer carton and protect from light.
- Do not freeze.
- Once opened, Granisetron should be used immediately.
- Once diluted Granisetron should be used immediately. If not used immediately, the ready to use solution should be stored at 25 ºC, protected from sunlight and used within 24 hours

Medicines should not be disposed 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 Granisetron contains:
Each ml of Granisetron concentrate for solution for injection/infusion contains 1 mg of granisetron (as the hydrochloride). Other ingredients are citric acid (monohydrate), hydrochloric acid, sodium chloride, sodium hydroxide, water for injections.
What Granisetron looks like and contents of the pack:
Granisetron is a clear colourless solution.
The pack may contain 5 or 10 clear glass ampoules. The ampoules contain either 1 ml or 3 ml Granisetron 1 mg/ ml concentrate for solution for injection/infusion. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer:

Marketing Authorisation Holder:

Fresenius Kabi Limited
Cestrian Court, Eastgate Way, Manor Park
Runcorn, Cheshire, WA7 1NT, UK

Manufacturers:

Labesfal –Laboratórios Almiro S.A (Fresenius Kabi Group)
Zona Industrial do Lagedo, 3465-157 Santiago de Besteiros, Portugal

And

Fresenius Kabi Austria GmbH, Hafnerstrass 36, A-8055 Graz, Austria
This medicinal product is authorised in the Member States of the EEA under the following names:

UK	Granisetron 1mg/ml concentrate for solution for injection/infusion
Austria	Granisetron Kabi 1 mg/ml Konzentrat zur Herstellung einer Injektionslösung/Infusionslösung
Belgium	Granisetron Fresenius Kabi 1 mg/ml, oplossing voor injectie/ infusie / solution injectable ou pour perfusion / Konzentrat zur Herstellung einer Injektionslösung/Infusionslösung
Czech Republic	Granisetron Kabi 1 mg/ml, koncentrát pro přípravu injekčního / infuzního roztoku
Germany	Granisetron Kabi 1 mg/ml Konzentrat zur Herstellung einer Injektionslösung/Infusionslösung
Greece	Granisetron Kabi, 1mg/ml, πυκνό διάλυμα για παρασκευή διαλύματος προς ένεση/έγχυση
Spain	Granisetron Kabi 1 mg/ml concentrado para solución inyectable / para perfusión
Finland	Granisetron Fresenius Kabi 1 mg/ml injektio-/infuusiokonsentraatti, liuosta varten
Hungary	Granisetron Kabi 1 mg/ml koncentrátum oldatos injekcióhoz vagy infúzióhoz
Italy	Granisetron Kabi 1 mg/ml Concentrato per soluzione iniettabile/ per infusione
Luxemburg	Granisetron Kabi 1 mg/ml Konzentrat zur Herstellung einer Injektionslösung/Infusionslösung
The Netherlands	Granisetron Fresenius Kabi 1 mg/ml, oplossing voor injectie/infusie
Portugal	Granissetrom Kabi
Romania	Granisetron Kabi 1 mg/ml, concentrat pentru soluţie injectabilă/ perfuzabilă
Sweden	Granisetron Fresenius Kabi 1 mg/ml koncentrat till injektions-/ infusionsvätska, lösning
Slovak Republic	Granisetron Kabi 1 mg/ml, injekčný alebo infúzny koncentrát

This leaflet was last approved in 21.11.2008

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The following information is intended for medical healthcare professionals only:

Instructions for dilution:

Dilute before use. For single use only. Any unused portion should be discarded. The diluted injections and infusions are to be inspected visually for particulate matter prior to administration. They should only be used if the solution is clear and free from particles.

Adults: The contents of a 1 ml ampoule can be diluted to a volume of 5 ml; the contents of a 3 ml ampoule can be diluted to a volume of 15 ml.

Granisetron can also be diluted in 20 to 50 ml compatible infusion fluid and then given over five minutes as an intravenous infusion in any of the following solutions:

0.9 % w/v sodium chloride injection
5 % w/v glucose injection
Lactated Ringer's Solution;

No other diluents should be used.

Children 2 years of age and older: To prepare the dose of 20 - 40 µg/kg, the appropriate volume is withdrawn and diluted with infusion fluid (as for adults) to a total volume of 10 to 30 ml.

As a general precaution, Granisetron should not be mixed in solution with other drugs.

Shelf life of the finished medicinal product:
2 years
Once opened the product should be used immediately.
Ideally, intravenous infusions of Granisetron should be prepared at the time of administration. After dilution, or when the container is opened for the first time, the shelf life is 24 hours when stored at ambient temperature (25ºC) in normal indoor illumination protected from direct sunlight. It must not be used after 24 hours. If to be stored after preparation, Granisetron infusions must be prepared under appropriate aseptic conditions.

Granisetron 1 mg / ml is compatible with Dexamethason dihydrogenphosphate dinatrium in a concentration of 10-60 µg/ml of Granisetron and 80-480 µg/ml Dexamethasonphosphate diluted in sodium chloride 0.9 % or Glucose 5 % solution over a period of 24 hours.

Special precautions for storage
Keep the ampoules in the outer carton in order to protect from light. Do not freeze. Any unused product or waste material should be disposed of in accordance with local requirements.

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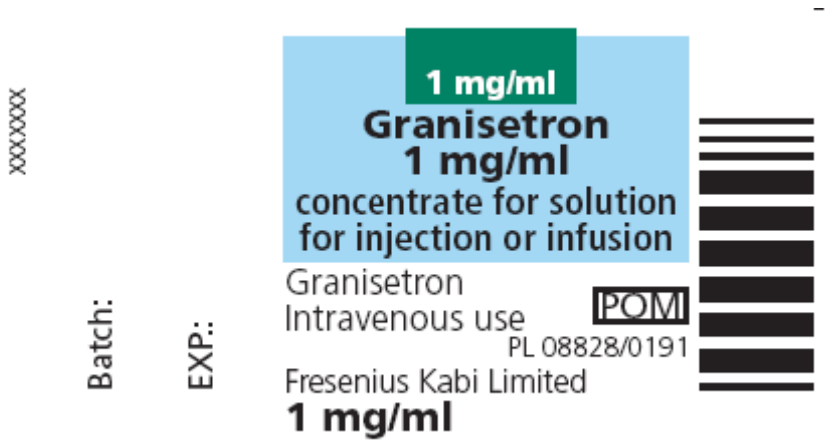
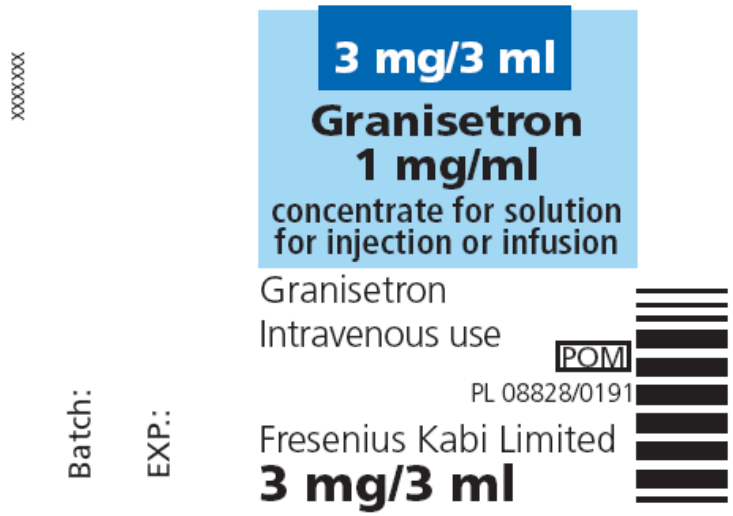
Module 4
Labelling

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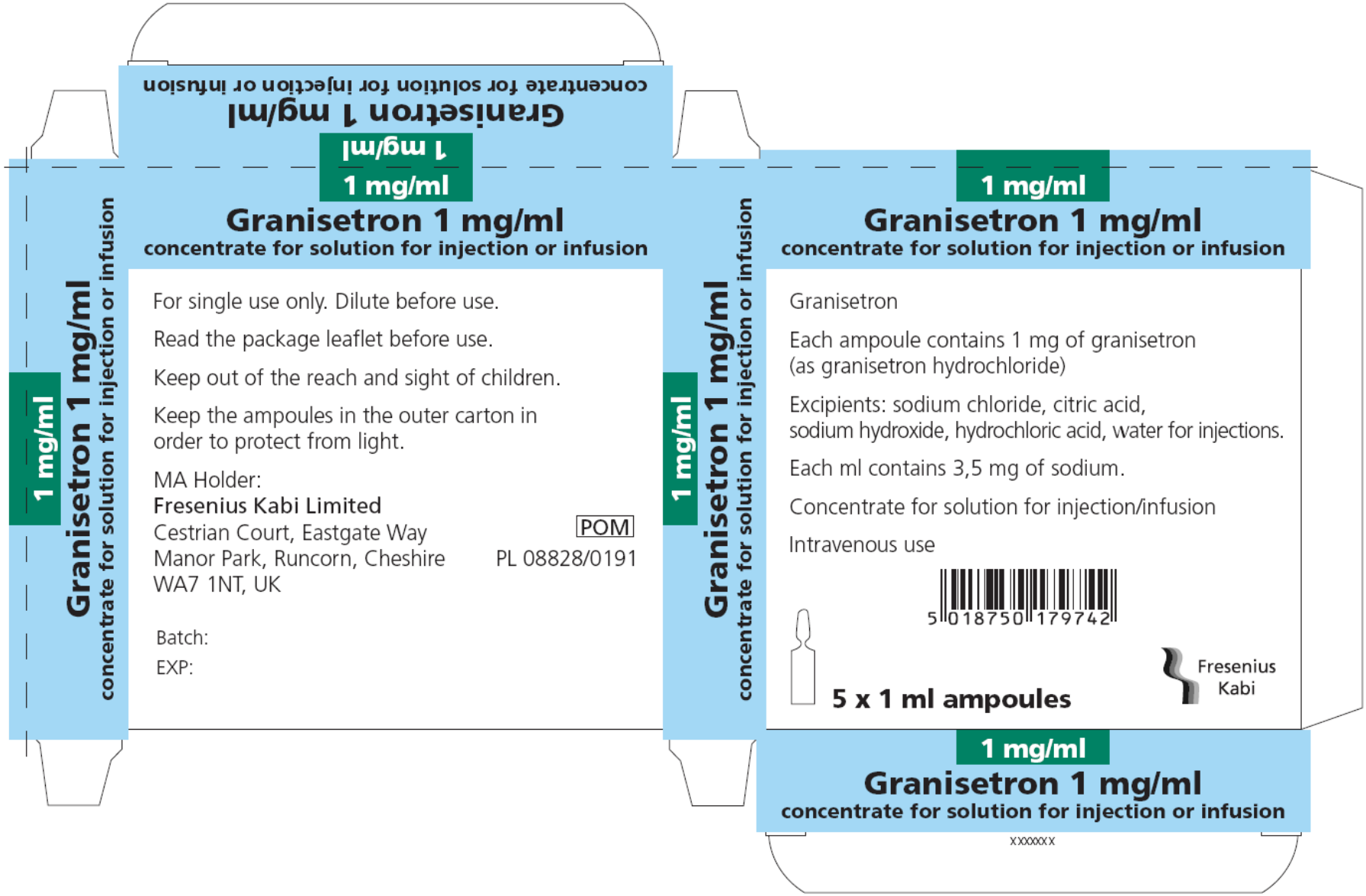
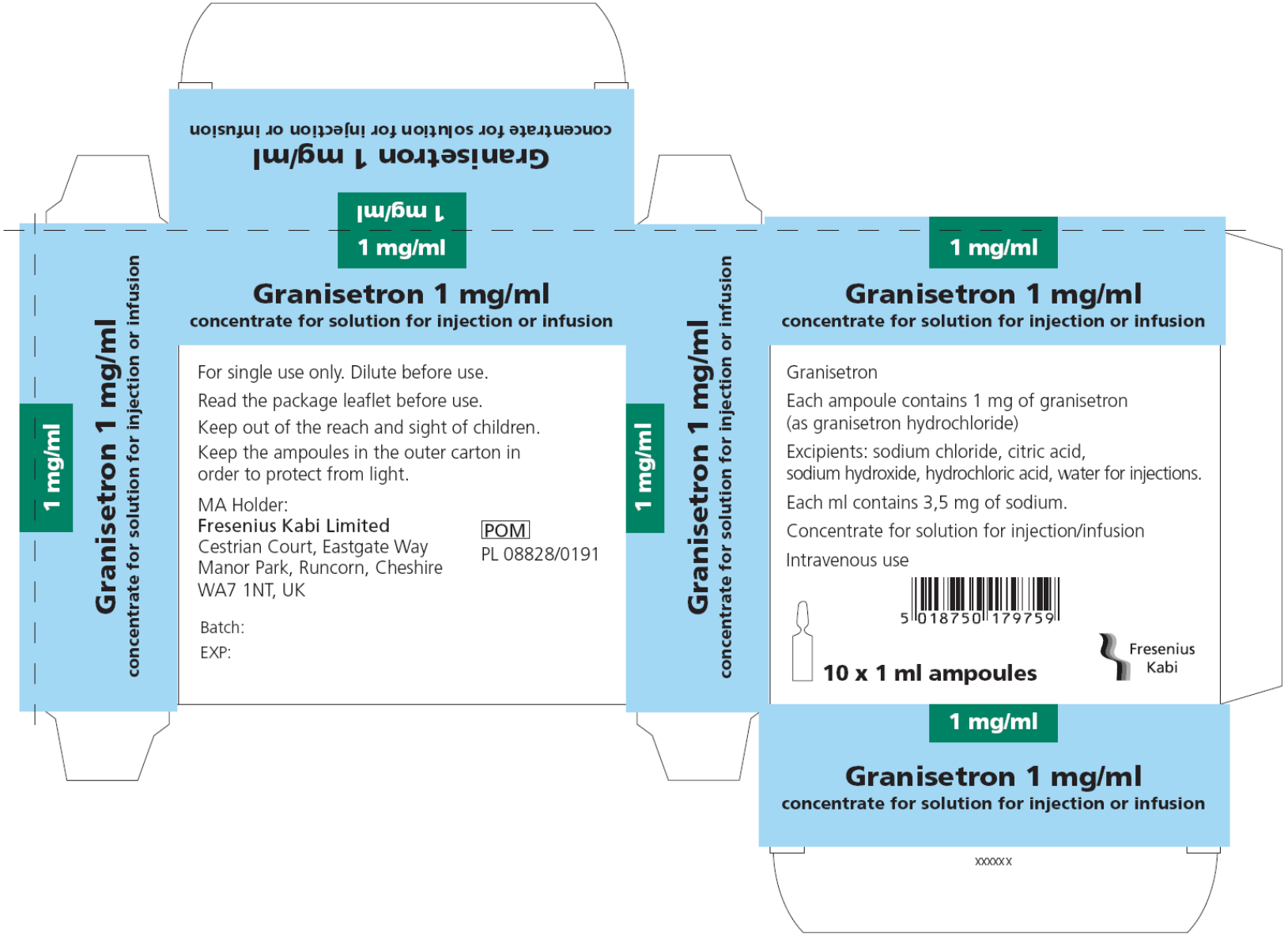
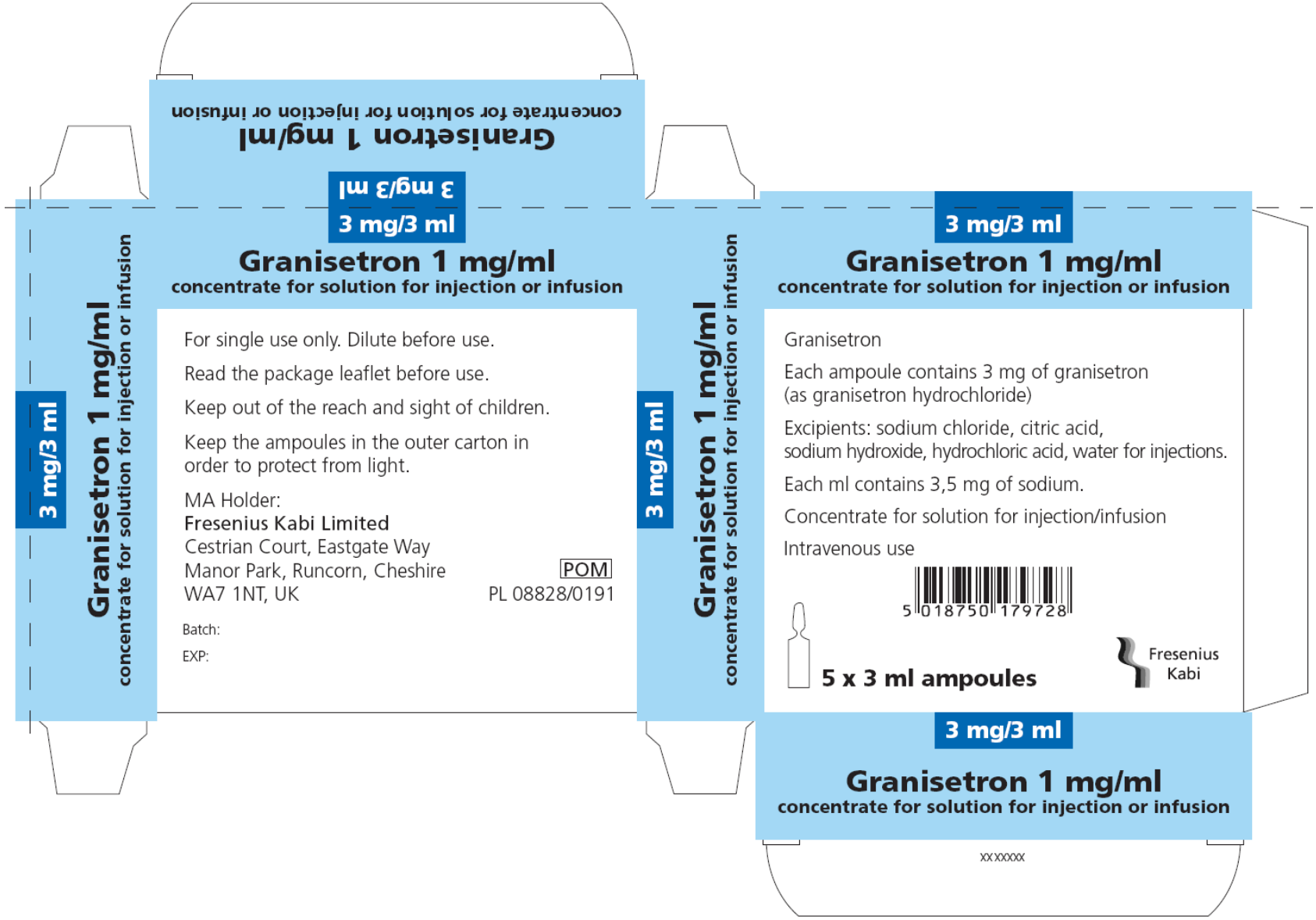
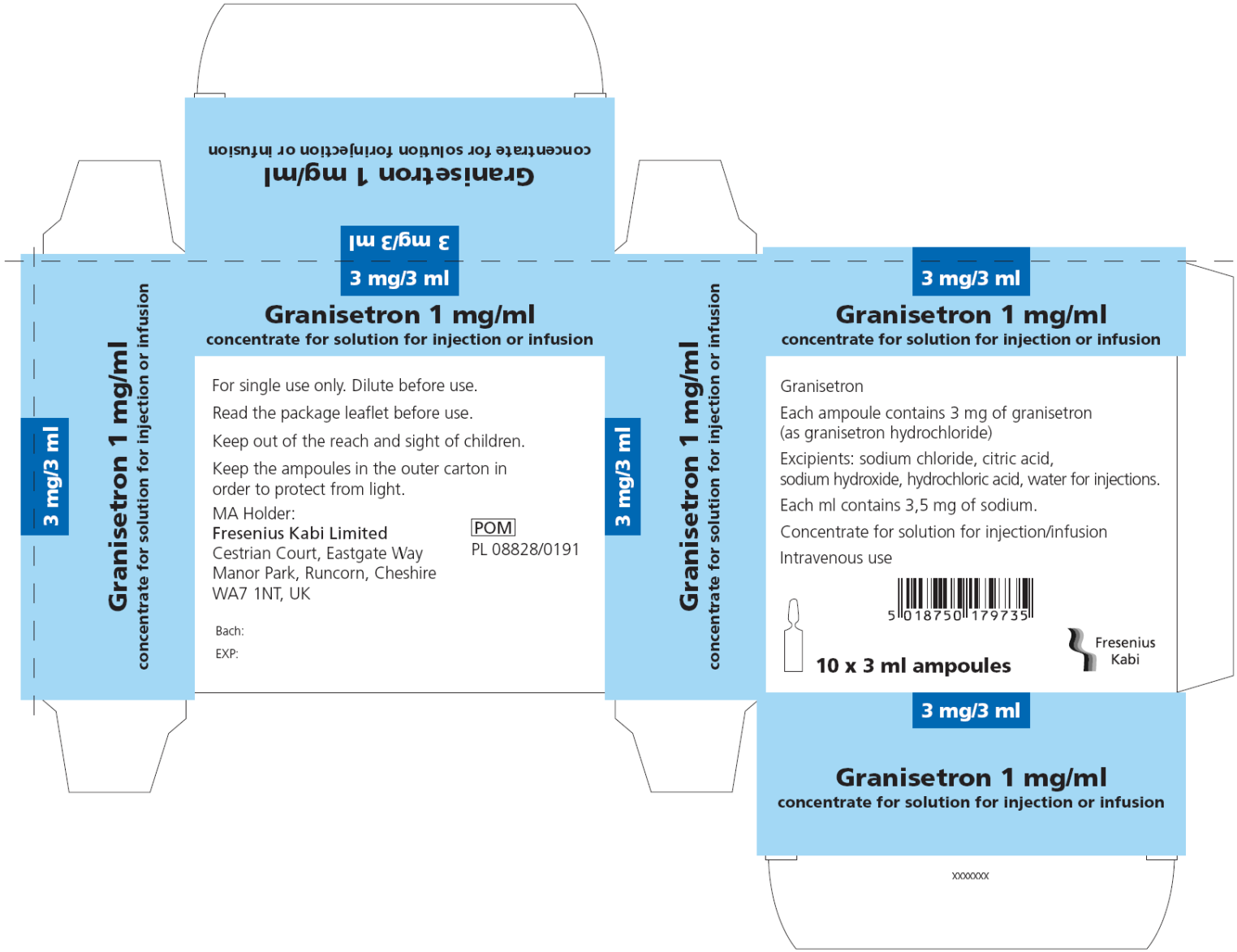
3 mg/3 ml
Granisetron
1 mg/ml
concentrate for solution
for injection or infusion
Granisetron
Intravenous use
POM
PL 08828/0191
Fresenius Kabi Limited
3 mg/3 ml


1 mg/ml
Granisetron 1 mg/ml
concentrate for solution for injection or infusion
1 mg/ml
Granisetron 1 mg/ml
concentrate for solution for injection or infusion
For single use only. Dilute before use.
Read the package leaflet before use.
Keep out of the reach and sight of children.
Keep the ampoules in the outer carton in order to protect from light.
MA Holder:
Fresenius Kabi Limited
Cestrian Court, Eastgate Way
Manor Park, Runcorn, Cheshire
WA7 1NT, UK
POM
PL 08828/0191
Batch:
EXP:
1 mg/ml
Granisetron 1 mg/ml
concentrate for solution for injection or infusion
1 mg/ml
Granisetron 1 mg/ml
concentrate for solution for injection or infusion
Granisetron
Each ampoule contains 1 mg of granisetron (as granisetron hydrochloride)
Excipients: sodium chloride, citric acid, sodium hydroxide, hydrochloric acid, water for injections.
Each ml contains 3,5 mg of sodium.
Concentrate for solution for injection/infusion
Intravenous use
5 018750 179742
5 x 1 ml ampoules
Fresenius Kabi
1 mg/ml
Granisetron 1 mg/ml
concentrate for solution for injection or infusion
xxxxxx


Granisetron 1 mg/ml
concentrate for solution for injection or infusion
1 mg/ml
Granisetron 1 mg/ml
concentrate for solution for injection or infusion
For single use only. Dilute before use.
Read the package leaflet before use.
Keep out of the reach and sight of children.
Keep the ampoules in the outer carton in order to protect from light.
MA Holder:
Fresenius Kabi Limited
Cestrian Court, Eastgate Way
Manor Park, Runcorn, Cheshire
WA7 1NT, UK
POM
PL 08828/0191
Batch:
EXP:
1 mg/ml
Granisetron 1 mg/ml
concentrate for solution for injection or infusion
1 mg/ml
Granisetron 1 mg/ml
concentrate for solution for injection or infusion
Granisetron
Each ampoule contains 1 mg of granisetron (as granisetron hydrochloride)
Excipients: sodium chloride, citric acid, sodium hydroxide, hydrochloric acid, water for injections.
Each ml contains 3,5 mg of sodium.
Concentrate for solution for injection/infusion
Intravenous use
5 018750 179759
10 x 1 ml ampoules
Fresenius Kabi
1 mg/ml
Granisetron 1 mg/ml
concentrate for solution for injection or infusion
xxxxxx


Granisetron 1 mg/ml
concentrate for solution for injection or infusion
3 mg/3 ml
3 mg/3 ml
Granisetron 1 mg/ml
concentrate for solution for injection or infusion
For single use only. Dilute before use.
Read the package leaflet before use.
Keep out of the reach and sight of children.
Keep the ampoules in the outer carton in order to protect from light.
MA Holder:
Fresenius Kabi Limited
Cestrian Court, Eastgate Way
Manor Park, Runcorn, Cheshire
WA7 1NT, UK
POM
PL 08828/0191
Batch:
EXP:
3 mg/3 ml
Granisetron 1 mg/ml
concentrate for solution for injection or infusion
3 mg/3 ml
Granisetron 1 mg/ml
concentrate for solution for injection or infusion
Granisetron
Each ampoule contains 3 mg of granisetron (as granisetron hydrochloride)
Excipients: sodium chloride, citric acid, sodium hydroxide, hydrochloric acid, water for injections.
Each ml contains 3,5 mg of sodium.
Concentrate for solution for injection/infusion
Intravenous use
5 018750 179728
5 x 3 ml ampoules
Fresenius Kabi
3 mg/3 ml
Granisetron 1 mg/ml
concentrate for solution for injection or infusion
XX XXXXX


Granisetron 1 mg/ml
concentrate for solution for injection or infusion
3 mg/3 ml
3 mg/3 ml
Granisetron 1 mg/ml
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For single use only. Dilute before use.
Read the package leaflet before use.
Keep out of the reach and sight of children.
Keep the ampoules in the outer carton in order to protect from light.
MA Holder:
Fresenius Kabi Limited
Cestrian Court, Eastgate Way
Manor Park, Runcorn, Cheshire
WA7 1NT, UK
POM
PL 08828/0191
Bach:
EXP:
3 mg/3 ml
Granisetron 1 mg/ml
concentrate for solution for injection or infusion
3 mg/3 ml
Granisetron 1 mg/ml
concentrate for solution for injection or infusion
Granisetron
Each ampoule contains 3 mg of granisetron (as granisetron hydrochloride)
Excipients: sodium chloride, citric acid, sodium hydroxide, hydrochloric acid, water for injections.
Each ml contains 3,5 mg of sodium.
Concentrate for solution for injection/infusion
Intravenous use
5 018750 179735
10 x 3 ml ampoules
Fresenius Kabi
3 mg/3 ml
Granisetron 1 mg/ml
concentrate for solution for injection or infusion
xxxxxx

Module 5
Scientific discussion during initial procedure

I INTRODUCTION

On 21st November 2008, Austria, Belgium, Czech Republic, Germany, Greece, Spain, Finland, Hungary, Italy, Luxembourg, The Netherlands, Portugal, Romania, Sweden, the Slovak Republic and the UK agreed to grant marketing authorisations to Fresenius Kabi Limited for the medicinal product Granisetron 1mg/ml Concentrate for Solution for Injection/Infusion. The licences were granted via the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS – UK/H/1439/001/DC). After the national phase, a licence was granted in the UK on 22nd January 2009 (PL 08828/0191).

This application was made under Article 10.1 of Directive 2001/83 EC for Granisetron 1mg/ml Concentrate for Solution for Injection/Infusion, containing the known active substance granisetron hydrochloride. The reference medicinal product for this application is Kytril Infusion 3mg/3ml (PL 00031/0594), which was originally licensed to Smithkline Beecham PLC in November 1991 and is now registered with Roche Products Limited (following a change of ownership in October 2001).

Granisetron is a potent anti-emetic and highly selective antagonist of 5-hydroxytryptamine (5-HT3) receptors with a negligible affinity for other receptor types including 5-HT and dopamine D2 binding sites. Granisetron is indicated for the prevention or treatment of nausea and vomiting induced by cytostatic therapy (chemotherapy and radiotherapy).

The proposed product is developed using an approved drug substance that is to be administered as an aqueous intravenous solution, containing the same drug substance in the same concentration as the reference product. Therefore, a bioequivalence study is not required in support of this application.

A formal Environmental Risk Assessment has not been performed as the product is intended for generic substitution. Hence, no increase in environmental risk is to be expected compared to that of the reference product.

An acceptable justification for not submitting a European Risk Management Plan has been provided. Other documentation relating to pharmacovigilance system has been provided.

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP certificates of satisfactory inspection summary reports, ‘close-out letters’ issued by the inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those non-Community sites.

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Granisetron 1mg/ml Concentrate for Solution for Injection/Infusion
Name(s) of the active substance(s) (USAN)	Granisetron hydrochloride
Pharmacotherapeutic classification (ATC code)	Antiemetics and antinauseants, Seretonin (5-HT3) (A04 AA02)
Pharmaceutical form and strength(s)	1mg/ml Solution for Injection
Reference numbers for the Mutual Recognition Procedure	UK/H/1439/001/DC
Reference Member State	United Kingdom
Member States concerned	Austria, Belgium, Czech Republic, Germany, Greece, Spain, Finland, Hungary, Italy, Luxembourg, The Netherlands, Portugal, Romania, Sweden and the Slovak Republic
Marketing Authorisation Number(s)	PL 08828/0191
Name and address of the authorisation holder	Fresnius Kabi Limited, Cestrian Court, Eastgate Way, Manor Park, Runcorn, Cheshire, WA7 1NT, UK

III SCIENTIFIC OVERVIEW AND DISCUSSION

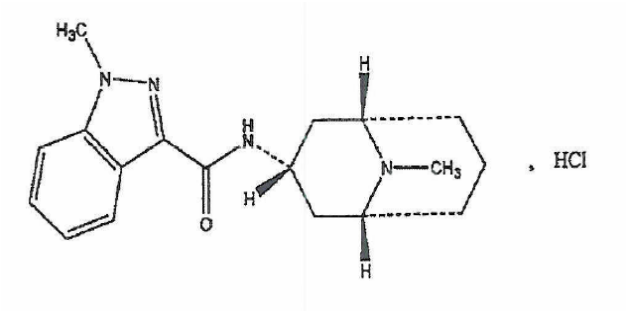
III.1 QUALITY ASPECTS

DRUG SUBSTANCE

INN: Granisteron hydrochloride

Chemical Names: 1-Methyl-N-[(lR,3R,5S)-9-methyl-9-azabicyclo[3.3.1]non-3-yl]-1H-indazole-3-carboxamide hydrochloride

Structure:



Molecular formula: $C_{18}H_{25}ClN_4O$

Molecular weight: 348.9

Physical form: A white or almost white powder freely soluble in water, sparingly soluble in methylene chloride, slightly soluble in methanol

Granisetron hydrochloride is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of granisteron hydrochloride are covered by a certificate of suitability for one of the active substance manufacturers. For the other active substance manufacturer, a drug master file has been submitted.

Synthesis of the drug substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant certificates of analysis. No materials of animal or human origin are used in the production of the active substance.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. All impurities have been appropriately characterised and certificates of analysis have been provided for any working standards used. Batch analysis data are provided that comply with the proposed specification.

Suitable specifications for all materials used in the active substance packaging have been provided. The primary packaging meets the requirements for materials in contact with food.

Appropriate stability data have been generated, from studies carried out in accordance with ICH conditions. A suitable retest period has been set, based on the stability data provided.

DRUG PRODUCT

Other ingredients

Other ingredients consist of pharmaceutical excipients citric acid monohydrate, hydrochloric acid (for pH adjustment), sodium chloride, sodium hydroxide (for pH adjustment) and water for injections. All excipients are controlled to their respective European Pharmacopoeia monograph. Satisfactory certificates of analysis have been provided for all excipients. None of the excipients used contain materials of animal or human origin.

Pharmaceutical development
Suitable pharmaceutical development data have been provided for this application.

Manufacture
A description and flow-chart of the manufacturing method have been provided. In-process controls are satisfactory based on process validation data and controls on the finished product. Process validation has been carried out on batches of the product. The results appear satisfactory.

Finished product specification
The finished product specification is satisfactory. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

Container Closure System
The finished product is supplied in either a 1ml or 3ml Type I clear glass ampoules, in pack sizes of 5 or 10 ampoules.

Specifications and certificates of analysis for the primary packaging material have been provided. These are satisfactory. All primary packaging is controlled to European Pharmacopoeia standards and complies with guidelines concerning materials in contact with parenteral products.

Stability
Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.

Based on the results, a shelf-life of 2 years has been set when the product is unopened, with the storage conditions "Keep the ampoules in the outer carton in order to protect from light. Do not freeze."

It has been stipulated that the contents of the vial should be used immediately after opening. However, the following instructions are also given concerning storage of the product after dilition:
Chemical and physical in-use stability has been demonstrated for 24 hours at 25ºC protected from direct sunlight.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

Summary of Product Characteristics (SPC), Patient Information Leaflet (PIL) and Labelling
The SPC, PIL and labelling are pharmaceutically satisfactory.

The applicant has submitted results of PIL user testing. The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

MAA Form
The MAA form is pharmaceutically satisfactory.

Expert Report
The pharmaceutical expert report is written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Conclusion
It is recommended that a Marketing Authorisation is granted for this application.

III.2 PRE-CLINICAL ASPECTS

GLP ASPECTS
Since a literature review has been presented, it is not known whether the studies cited were conducted in accordance with the Good Laboratory Practice (GLP) regulations. However, it is assumed that the studies conducted by the innovator would have been in compliance with the standards prevailing at the time.

PHARMACODYNAMICS
The applicant has provided a thorough review of the functions of 5-HT receptors, the mode of action of 5-HT_3 antagonists and the physiology of emesis. A thorough review of the data on granisetron and other 5-HT_3 antagonists is also presented. Since the properties of granisetron in relation to the proposed indications are well known, these data will not be re-assessed here.

Granisetron is a potent and selective 5-hydroxytryptamine (5-HT_3) receptor antagonist with anti-emetic activity in animal models and in patients. Selective antagonism of 5-HT_3 receptors by granisetron has been observed in rat and guinea-pig brain. In the ferret, cisplatin produced emesis and this was blocked by granisetron.

No new pre-clinical pharmacology data have been found that would alter the risk-benefit for granisetron.

PHARMACOKINETICS
Pre-clinical data have been cited, supplemented with human data. All data are from literature sources. No new pre-clinical pharmacokinetic information or data that alter the profile for granisetron have been found from the applicant's literature search.

TOXICOLOGY
The toxicity of the 5-HT_3 receptor antagonists is low. There is no evidence of mutagenic or teratogenic effects or specific organ toxicities. Only in long-term studies using higher dosages have rodents exhibited liver parenchymal changes of the type often observed on administration of drugs metabolised by the cytochrome P450 system.

The data from the UDS Physician's Desk Reference on mutagenesis, carcinogenesis and impairment of fertility have been presented. The carcinogenicity seen in rodents with granisetron has been well-documented.

The data on experiments on the hERG channel with 5-HT_3 antagonists is presented and suitable mention of this has been made in Section 5.3 of the SPC, as for other recent marketing applications for 5-HT_3 antagonists.

The Non-clinical Overview also contains a review of human safety data.

EXCIPIENTS
All the excipients are commonly used in injectable formulations and comply with the European Pharmacopoeia, as does the drug substance.

IMPURITIES
A suitable justification has been provided for the limits of all impurities in the specifications. All limits comply with the ICH guidelines.

ENVIRONMENTAL RISK ASSESSMENT
The applicant has not conducted a formal Environmental Risk Assessment (ERA). Since the product is a generic medicinal product intended to replace the originator, it is not anticipated that it will increase the amount of granisetron and its break-down products in the environment. This is acceptable.

SUMMARY OF PRODUCT CHARACTERISTICS (SPC)
The SPC is satisfactory from a preclinical viewpoint.

NON-CLINICAL EXPERT REPORT
The non-clinical expert report has been written by an appropriately qualified person and is a suitable summary of the preclinical aspects of the dossier.

OVERALL CONCLUSION ON THE NON-CLINICAL PART
The applicant has provided a thorough review of the non-clinical and clinical data. No new data have been found that would alter the risk-benefit for granisetron. The formulation is a simple solution and it is accepted that essential similarity has been demonstrated.

There are no non-clinical objections to the grant of a licence.

III.3 CLINICAL ASPECTS

Pharmacokinetics
No new data have been submitted and none are required for an application of this type.

Pharmacokinetic data submitted from literature sources show wide inter-subject differences in plasma half-life and total plasma clearance among individual healthy volunteers and cancer patients. Nevertheless, the pharmacokinetics of granisetron are consistent with the use of granisetron as a single-dose anti-emetic administered immediately prior to chemotherapy. Linear pharmacokinetics with generally rapid elimination combined with good tolerability contributes to a good safety profile for the drug. Granisetron has been shown to be consistently effective, with a long duration of action. The variability in pharmacokinetic parameters does not appear to adversely affect efficacy because no clear relationship between plasma concentrations and anti-emetic effect is apparent. No dosage adjustments appear necessary because of age, site of malignancy, or renal or hepatic status.

According to CPMP guidelines, the applicant is not required to submit a bioequivalence study if the product is to be administered as an aqueous intravenous solution containing the same active substance, in the same concentration as the currently authorised product (CPMP/EWP/1401/98, subpoint 5.1.6, Parenteral solutions).

Based on the data provided, Granisetron 1mg/ml concentrate for solution for infusion is considered bioequivalent with Kytril Ampoules 1mg/ml Concentrate for solution for infusion or injection, Roche Products Limited, UK.

Pharmacodynamics
No new data have been submitted and none are required for an application of this type.

Clinical efficacy
No new data have been submitted and none are required for an application of this type.

Clinical safety
No new safety data are supplied or required for this generic application.

Summary of Product Characteristics (SPC), Patient Information Leaflet (PIL) and labelling
The SPC, PIL and labelling are medically satisfactory and consistent with those for the reference products.

Clinical Expert Report
The clinical expert report is written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

MAA Form
The MAA Form is medically satisfactory.

Clinical Conclusion
The grant of a marketing authorisation is recommended.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY

The important quality characteristics of Granisetron 1mg/ml Concentrate for Solution for Injection/Infusion are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRE-CLINICAL

The pre-clinical data submitted have not revealed any evidence of potential risks to human health from treatment with Granisetron 1mg/ml Concentrate for Solution for Injection/Infusion beyond those already described.

EFFICACY

No new data have been submitted and none are required for an application of this type.

Granisetron 1mg/ml Concentrate for Solution for Injection/Infusion is the generic version of Kytril Infusion 3mg/3ml (PL 00031/0594). The use of the reference product is well-established in the UK. Both products contain the same quantitative and qualitative composition of the active ingredient, granisetron hydrochloride.

According to CPMP guidelines, the applicant is not required to submit a bioequivalence study if the product is to be administered as an aqueous intravenous solution containing the same active substance, in the same concentration as the currently authorised product (CPMP/EWP/1401/98, subpoint 5.1.6, Parenteral solutions).

No new safety data are supplied or required for this generic application. Granisetron hydrochloride has a well-established side-effect profile and is generally well-tolerated.

The SPC, PIL and labelling are satisfactory.

BENEFIT-RISK ASSESSMENT

The quality of the product is acceptable, and no new preclinical or clinical safety concerns have been identified. The data supplied supports the claim that the applicant's product and the innovator product are interchangeable. Extensive clinical experience with granisetron hydrochloride is considered to have demonstrated the therapeutic value of the compound. The risk-benefit is, therefore, considered to be positive.

Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome