Safeguarding public health

MHRA

Public Assessment Report

Decentralised Procedure

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

UK/H/1929/001/DC
UK licence no: PL 32835/0001

axios Pharma GmbH

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

LAY SUMMARY

On 5th March 2009, Austria, Germany and the UK agreed to a grant marketing authorisation to axios Pharma GmbH for the medicinal product Granisetron 1mg/ml Concentrate for Solution for Injection or 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 30th March 2009.

Granisetron 1 mg/ml belongs to a group of medicines called 5-HT_3 receptor antagonists which act as anti-emetics.

It is used to prevent and treat the nausea (feeling sick) and vomiting (being sick) that may occur after treatment with anticancer medicines (chemotherapy) or with radiation therapy.

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 or Infusion outweigh the risks, hence a Marketing Authorisation has been granted.

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Module 1

Product Name	Granisetron 1mg/ml Concentrate for Solution for Injection or Infusion
Type of Application	Generic application, Article 10.1
Active Substance	Granisetron hydrochloride
Form	Concentrate for solution for injection or infusion
Strength	1mg/ml concentrate for solution for injection or infusion
MA Holder	axios Pharma GmbH, Hauptstrasse 198, D-33647 Bielefeld, Germany
RMS	UK
CMS	Austria, Germany
Procedure Number	UK/H/1929/001/DC
Timetable	Day 210 – 5th March 2009

Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Granisetron 1 mg/ml concentrate for solution for injection or infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
1 ml concentrate for solution for injection or infusion contains 1.12 mg granisetron hydrochloride equivalent to 1 mg granisetron.

3 ml concentrate for solution for injection or infusion contains 3.36 mg granisetron hydrochloride equivalent to 3 mg granisetron.

Excipients:
Up to 4.5 mg of sodium per 1 ml solution

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Concentrate for solution for injection or infusion

The product is a clear and colourless solution. The pH value of the solution is adjusted to 5 (nominal range: 4 – 6), its osmolality is 318 mOsmol/kg.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Granisetron 1 mg/ml is indicated for the prevention or treatment of nausea and vomiting induced by chemotherapy or radiotherapy in adults and children, 2 years of age and older.

4.2 Posology and method of administration
Granisetron 1 mg/ml is for intravenous administration only.

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

For further instructions regarding preparation see section 6.6.

Prevention
The recommended dose of Granisetron 1 mg/ml 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 1 mg/ml 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 1 mg/ml should be completed prior to the start of cytostatic therapy.

Treatment
The same dose of Granisetron 1 mg/ml as for prevention should be used for treatment. Additional doses should be administered at least 10 minutes apart.

Maximum daily dose
Up to three doses of 3 mg Granisetron 1 mg/ml may be administered within a 24-hour period. The maximum dose of Granisetron 1 mg/ml to be administered over 24 hours should not exceed 9 mg.

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

Children 2 years of age and older
Prevention
A single dose of Granisetron 1 mg/ml of 20 – 40 µg/kg body weight (up to 3 mg) should be administered by intravenous infusion, diluted in10 mL to 30 mL of compatible infusion fluid and administered over 5 minutes.

For further instructions regarding preparation see section 6.6.

Administration should be completed prior to the start of cytostatic therapy.

Treatment
The same dose of Granisetron 1 mg/ml as above should be used for treatment as prevention.

An additional dose of 40 µg/kg (up to 3 mg) 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 1 mg/ml should not be used in children below 2 years of age.

Elderly
No special requirements apply to elderly patients.

Patients with renal or hepatic impairment
No special requirements apply to those patients with renal or hepatic impairment.

4.3 Contraindications
Hypersensitivity to granisetron, to related substances (e.g. ondansetron) or to any of the excipients of Granisetron 1 mg/ml (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 1 mg/ml should be monitored carefully.

No special precautions are required for elderly patients or renally and/or hepatically impaired patients. 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.

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.

This medicinal product contains up to 4.5 mg sodium per 1 ml solution. This should 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.

Granisetron injections have been safely administered in patients treated with benzodiazepines, neuroleptics and anti-ulcer medications and is commonly prescribed with antiemetic treatments. 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 of Granisetron 1 mg/ml in human pregnancy. Therefore Granisetron 1 mg/ml 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 1 mg/ml in breast milk. Breast feeding should therefore be discontinued during therapy.

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 1 mg/ml 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 1 mg/ml is a potent anti-emetic and highly selective antagonist of 5-hydroxytryptamine (5 HT3) receptors. Radioligand binding studies have demonstrated that Granisetron 1 mg/ml has negligible affinity for other receptor types including 5 HT and dopamine D2 binding sites.

Granisetron 1 mg/ml 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 mcg/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 3 L/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 antiemetic 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 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 safety pharmacology, 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. 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. If changes do occur, they are generally without clinical significance. 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 ECG trace.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Citric acid monohydrate
Sodium hydroxide (for pH adjustment)
Water for injection

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

3 years

The product should be used immediately after opening. For single use only. Discard any remaining portion.

After Dilution:
Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C in normal indoor illumination protected from direct sunlight. From a microbiological point of view, the product should be used immediately. If to be stored, the dilutions should be prepared under appropriate aseptic conditions.

6.4 Special precautions for storage

Do not store above 25°C.
Do not freeze.
Keep the ampoules in the outer carton in order to protect from light.
For storage conditions of the diluted medicinal product see section 6.3.

6.5 Nature and contents of container

1 and 3 ml colourless ampoules.
Pack sizes: 5 x 1 ml, 10 x 1 ml, 5 x 3 ml and 10 x 3 ml

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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 1 mg/ml 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
0.18 % w/v sodium chloride and 4% glucose injection
5 % w/v glucose injection
Hartmann's solution
1.87 % w/v sodium lactate injection
10% mannitol injection

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 1 mg/ml should not be mixed in solution with other drugs

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

7 MARKETING AUTHORISATION HOLDER

axios Pharma GmbH
Hauptstrasse 198

D-33647 Bielefeld
Germany

8 MARKETING AUTHORISATION NUMBER(S)
PL 32835/0001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
30/03/2009

10 DATE OF REVISION OF THE TEXT
30/03/2009

Module 3

PACKAGE LEAFLET: INFORMATION FOR THE USER
Granisetron hydrochloride

axios PHARMA GMBH

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

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

In this leaflet:

1. WHAT GRANISETRON IS AND WHAT IT IS USED FOR

Granisetron belongs to a group of medicines called 5-HT_3 receptor antagonists which act as anti-emetics.

It is used to prevent and treat the nausea (feeling sick) and vomiting (being sick) that may occur after treatment with anticancer medicines (chemotherapy) or with radiation therapy.

Granisetron may be administered to adults, adolescents and children of at least two years of age.

2. BEFORE YOU USE GRANISETRON

Do not use Granisetron
- if you are **allergic** (hypersensitive) to granisetron, to any of the other ingredients in Granisetron or to any medicinal products acting like Granisetron (like other 5-HT_3 receptor antagonists, such as ondansetron)
- in **children under 2 years** of age, because insufficient experience is available.

Take special care with Granisetron
- if you have been told by a doctor that your **bowels** don't work properly
- if you have any **pain in your abdomen** (tummy) or your abdomen feels distended or swollen after having taken Granisetron
- if you have **severe constipation**.
- if you are on a **low sodium diet** (one ml of the drug contains up to 4.5 mg of sodium)
- if you have heart rhythm disorders

Please note:

Children

This medicine has been tested in children 2 years of age and older who were treated with anticancer medicines. In effective doses it has not been shown to cause other side effects or problems than it does in adults.

Elderly

This medicine has been tested in a limited number of patients 65 years of age or older and has not been shown to cause any other side effects or problems in older people than it does in younger adults.

Taking other medicines

You should tell your doctor if you are taking any of the following:
- medicines to treat heart rhythm disorders, beta-blockers as granisetron may affect the way your heart beats.
- ketoconazole (an antifungal) and phenobarbital (an antiepileptic) may influence the way your body handles granisetron.

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Using Granisetron with food and drink

You don't have to pay any special attention with food and drink.

Pregnancy and breast-feeding

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

Pregnacy

There is not enough information on the use of Granisetron in pregnancy for possible harmful effects to be evaluated. Granisetron should only be used in pregnancy following consultation with your doctor. Tell your doctor if you are pregnant or intending to become pregnant

Breast-feeding

It is not known whether Granisetron enters breast milk and therefore breast feeding should be discontinued during therapy.

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
1 ml of Granisetron contains up to 4.5 mg of sodium. **If you are on a controlled sodium diet, please contact your doctor immediately.**

3. HOW TO USE GRANISETRON

Dosage
The usual doses are:

Prevention and treatment of nausea and vomiting after cancer chemotherapy or radiation therapy

In adults: The recommended dose is 1 mg or 3 mg depending on the kind of chemotherapy or radiotherapy. To stop any sickness that may occur after the treatment, the same dose may be given to you for up to two more times within 24 hours if needed.
No more than 9 mg should be given to you in one day.

In children: The dose is based on the body weight and must be determined by your doctor: 0.02 – 0.04 mg for each kilogram (kg) of body weight (up to 3 mg) to prevent sickness before anticancer treatment. An additional dose of 40 µg/kg (up to 3 mg) may be administered within a 24 hour period either as a single dose or as two divided doses.

Method and route of administration
Usually Granisetron will be given to you by your doctor or nurse, before or during the treatment that is likely to make you feel sick. It can also be given afterwards to you to stop any sickness you may be having.
In adults Granisetron can be given diluted as an intravenous injection (into a vein) during 30 seconds or as an intravenous infusion (over a longer time).
In children Granisetron can be given as an intravenous infusion diluted in infusion fluid over five minutes.

If you use more Granisetron than you should or if you forget to use Granisetron
Since Granisetron will be applied to you by a doctor or nurse, it is unlikely that you will be given too much or that you will miss a dose.

Further questions

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

For information intended for medicinal or healthcare professionals please see accordant section below.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Granisetron can cause side effects, although not everybody gets them.

If the following happens, tell your doctor immediately:

- an allergic reaction causing swelling of the face, lips, tongue or throat, difficulty breathing or swallowing, rash or itching.

This is a very serious but rare side effect. You may need urgent medical attention.

The following side effects have been reported:

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), sleepiness (somnolence)
- Dizziness
- Weakness (asthenia)
- Diarrhoea
- Constipation
- Abdominal pain
- Reduced appetite
- 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):
- Abnormal heart rhythm
- Chest pain
- Shaking or muscular stiffness
- Abnormal body movement
- 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)
- Loss of appetite

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 or pharmacist.

5. HOW TO STORE GRANISETRON

Keep out of the reach and sight of children.
Do not store above 25°C.
Do not freeze.
Keep the ampoules in the outer carton.

Do not use Granisetron after the expiry date which is stated on the ampoule label and the outer carton after "Exp. Date". The expiry date refers to the last day of that month.

Do not use Granisetron if you notice the solution is not clear or free from particles.

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 Granisetron contains

The **active substance** is granisetron hydrochloride

Each 1 ml ampoule contains a total content of 1 mg granisetron as the hydrochloride in 1 ml of a sterile solution.

Each 3 ml ampoule contains a total content of 3 mg granisetron as the hydrochloride in 3 ml of a sterile solution.

The **other ingredients** are sodium chloride, citric acid monohydrate, sodium hydroxide and water for injections.

What Granisetron looks like and contents of the pack

Granisetron is a clear colourless concentrate for solution for injection or infusion.

Pack size:
Granisetron is available in packs of five or ten ampoules filled with 1 ml or 3 ml of the solution.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:
axios Pharma GmbH
Hauptstrasse 198
D-33647 Bielefeld, Germany

Distributer:
Apocare Pharma GmbH
Hauptstrasse 198
D-33647 Bielefeld, Germany

Manufacturer:
Apocare Pharma GmbH
Hauptstrasse 198
D-33647 Bielefeld, Germany

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

Austria and Germany:
axigran 1 mg/ml, Konzentrat zur Herstellung einer Injektions- oder Infusionslösung

United Kingdom:
Granisetron 1 mg/ml concentrate for solution for injection or infusion

This leaflet was last approved in 03/2009

The following information is intended for medicinal or healthcare professionals only:

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

It is important that you read the entire contents of this guide prior to the preparation of this medicinal product.

1. PRESENTATION

Granisetron is supplied as a concentrate for solution for intravenous injection or infusion in colourless glass ampoules with a volume of 1 ml or 3 ml containing a sterile, clear colourless solution.

2. PREPARATION FOR THE INTRAVENOUS ADMINISTRATION

In adults, Granisetron can be administered as an intravenous bolus over not less than 30 seconds diluted with infusion fluid. 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 infusion fluid and then given over 5 minutes as an intravenous infusion.

In children, Granisetron should be diluted to a total volume of 10 ml to 30 ml and administered by intravenous infusion over 5 minutes.

Granisetron is compatible with following solutions:

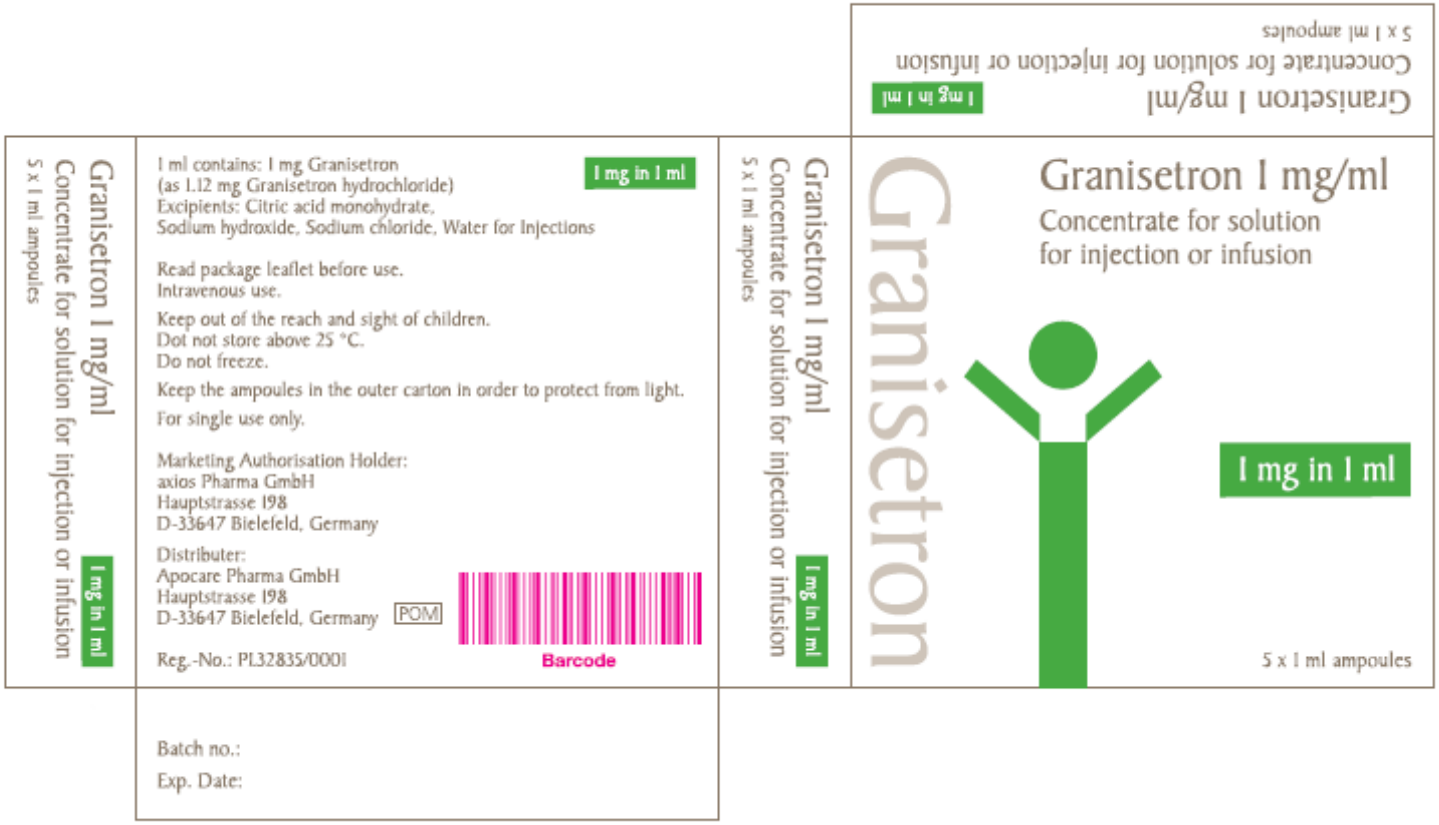
0.9 % w/v sodium chloride injection
0.18 % w/v sodium chloride and 4% glucose injection
5 % w/v glucose injection
Hartmann's solution
1.87 % w/v sodium lactate injection
10% mannitol injection

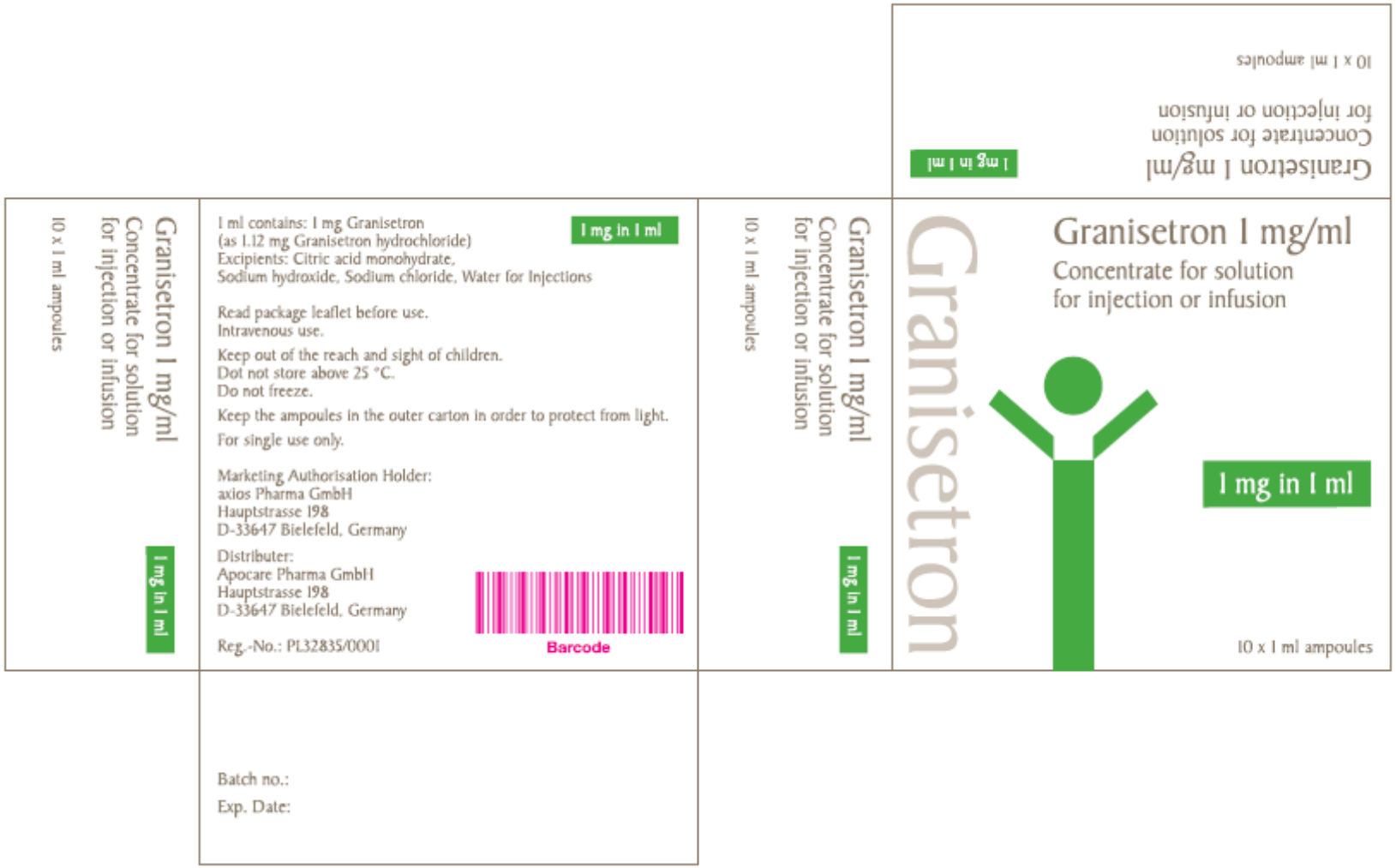
If required, Granisetron should only be diluted with one of these infusion fluids.
Granisetron must not be mixed with any other medicinal products.

For single use only. The product should be used immediately after opening the ampoule. Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C in normal indoor illumination protected from direct sunlight. From a microbiological point of view, the product should be used immediately. If to be stored, the dilutions should be prepared under appropriate aseptic conditions.
Do not store above 25 °C.
Do not freeze.
Keep the ampoules in the outer carton in order to protect from light.

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

Module 4
Labelling




Granisetron 1 mg/ml
Concentrate for solution
for injection or infusion
10 x 1 ml ampoules
1 mg in 1 ml
Granisetron
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Concentrate for solution
for injection or infusion
1 mg in 1 ml
10 x 1 ml ampoules
1 ml contains: 1 mg Granisetron
(as 1.12 mg Granisetron hydrochloride)
Excipients: Citric acid monohydrate,
Sodium hydroxide, Sodium chloride, Water for Injections
1 mg in 1 ml
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Distributer:
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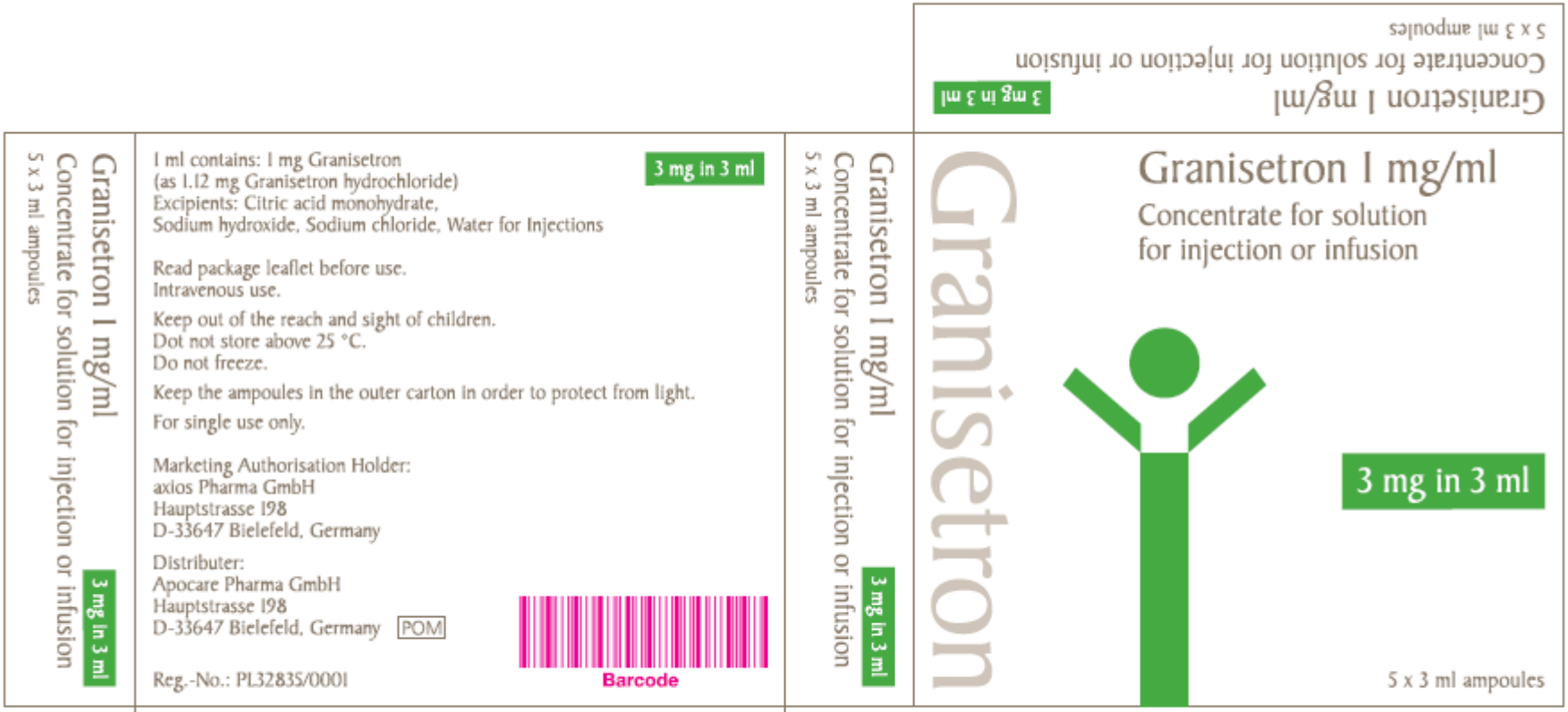
D-33647 Bielefeld, Germany
Reg.-No.: PL32835/0001
Barcode
Granisetron 1 mg/ml
Concentrate for solution
for injection or infusion
10 x 1 ml ampoules
1 mg in 1 ml
Batch no.:
Exp. Date:


Granisetron 1 mg/ml
Concentrate for solution for injection or infusion
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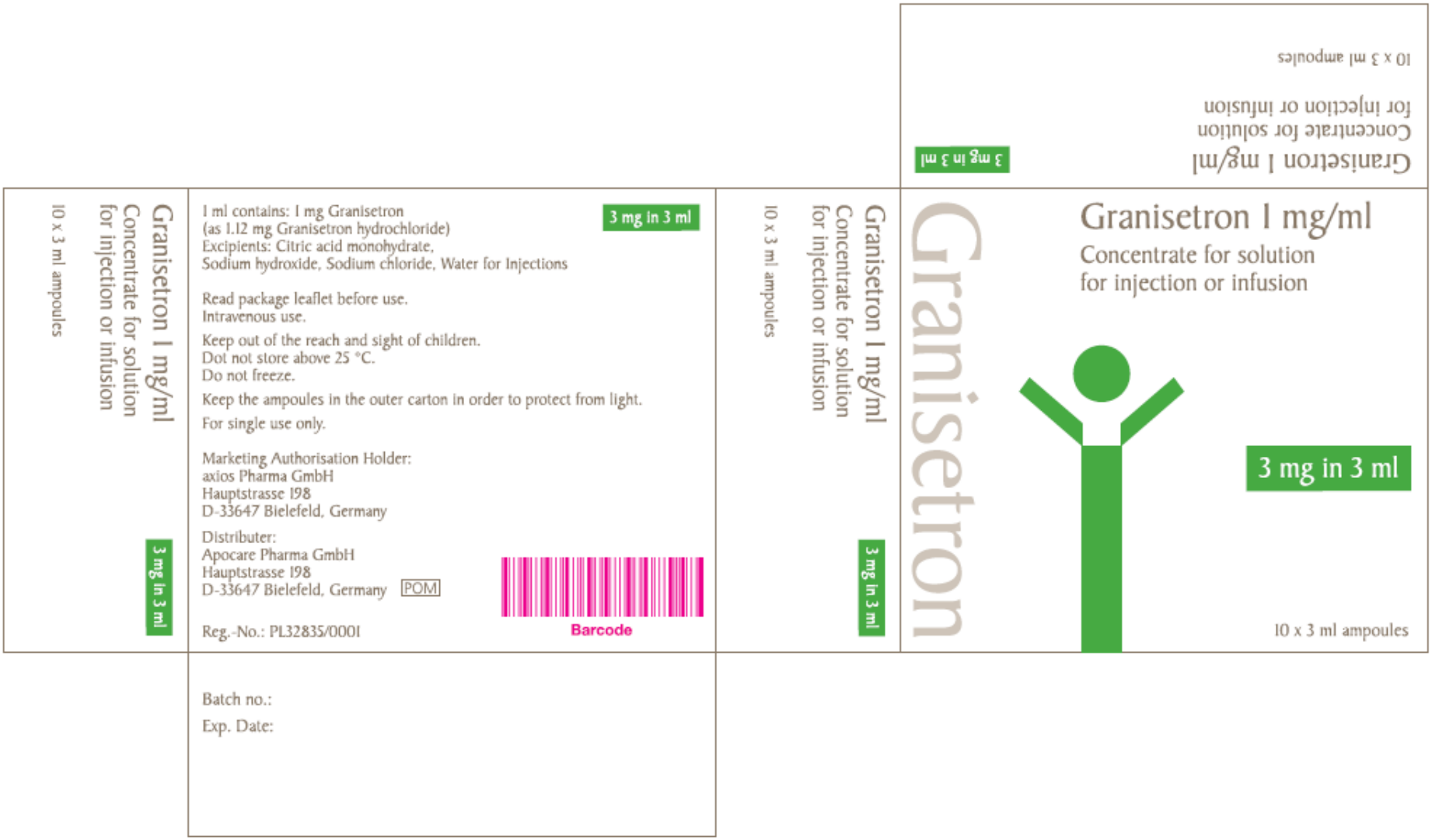
POM
Reg.-No.: PL32835/0001
Barcode
Batch no.:
Exp. Date:
Granisetron
Granisetron 1 mg/ml
Concentrate for solution
for injection or infusion
3 mg in 3 ml
5 x 3 ml ampoules


Granisetron 1 mg/ml
Concentrate for solution
for injection or infusion
10 x 3 ml ampoules
3 mg in 3 ml
Granisetron
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Concentrate for solution
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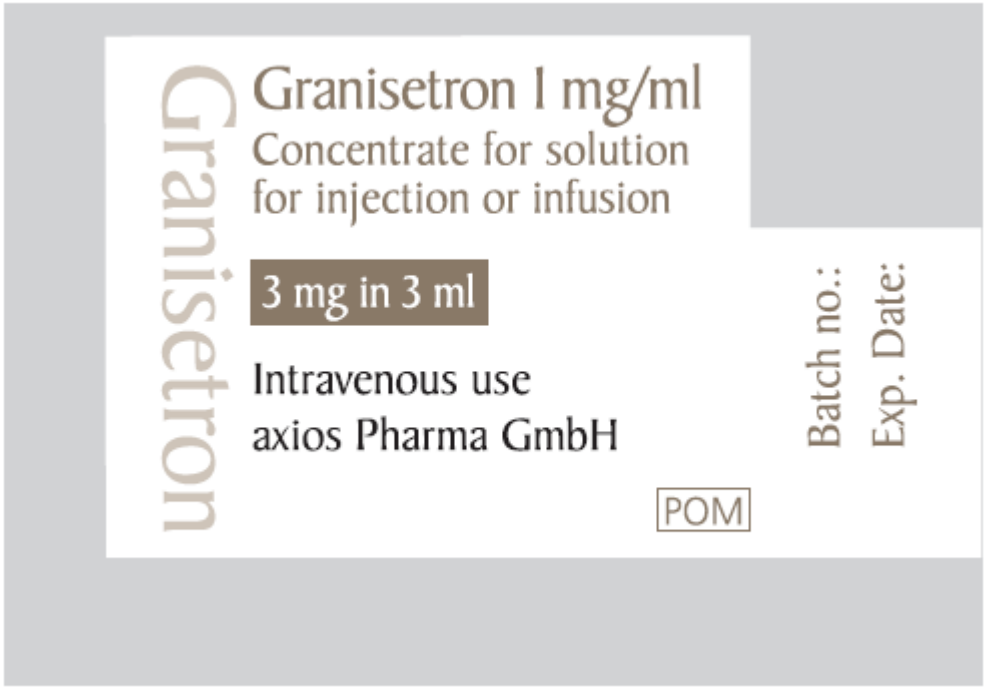
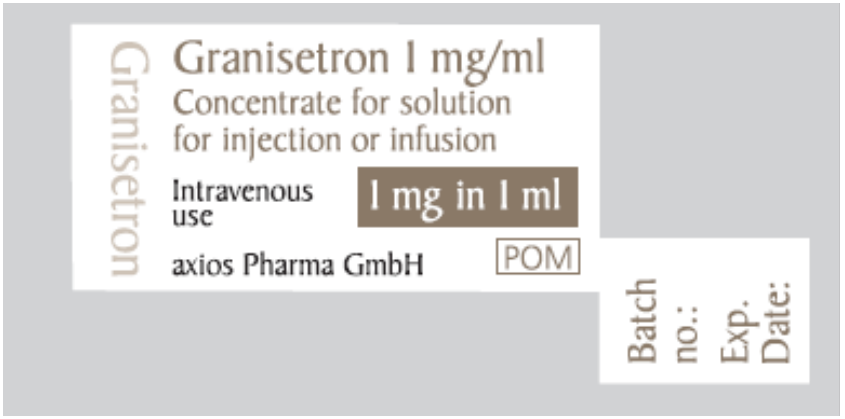
3 mg in 3 ml
1 ml contains: 1 mg Granisetron
(as 1.12 mg Granisetron hydrochloride)
Excipients: Citric acid monohydrate,
Sodium hydroxide, Sodium chloride, Water for Injections
3 mg in 3 ml
Read package leaflet before use.
Intravenous use.
Keep out of the reach and sight of children.
Dot not store above 25 °C.
Do not freeze.
Keep the ampoules in the outer carton in order to protect from light.
For single use only.
Marketing Authorisation Holder:
axios Pharma GmbH
Hauptstrasse 198
D-33647 Bielefeld, Germany
Distributer:
Apocare Pharma GmbH
Hauptstrasse 198
D-33647 Bielefeld, Germany
POM
Reg.-No.: PL32835/0001
Barcode
Batch no.:
Exp. Date:


Granisetron
Granisetron 1 mg/ml
Concentrate for solution
for injection or infusion
3 mg in 3 ml
Intravenous use
axios Pharma GmbH
POM
Batch no.:
Exp. Date:


Granisetron
Granisetron 1 mg/ml
Concentrate for solution
for injection or infusion
Intravenous use
1 mg in 1 ml
axios Pharma GmbH
POM
Batch no.:
Exp. Date:

Module 5
Scientific discussion during initial procedure

I INTRODUCTION

On 5th March 2009, Austria, Germany and the UK agreed to a grant marketing authorisation to axios Pharma GmbH for the medicinal product Granisetron 1mg/ml Concentrate for Solution for Injection or 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 30th March 2009.

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-HT_3) receptors with a negligible affinity for other receptor types including 5-HT and dopamine D_2 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 or Infusion
Name(s) of the active substance(s) (USAN)	Granisetron hydrochloride
Pharmacotherapeutic classification (ATC code)	Antiemetics and antinauseants, Seretonin (5-HT3) antagonists (A04 AA02)
Pharmaceutical form and strength(s)	1mg/ml Concentrate for Solution for Injection or Infusion
Reference numbers for the Mutual Recognition Procedure	UK/H/1929/001/DC
Reference Member State	United Kingdom
Member States concerned	Austria, Germany
Marketing Authorisation Number(s)	PL 32835/0001
Name and address of the authorisation holder	axios Pharma GmbH, Hauptstrasse 198, D-33647 Bielefeld, Germany

III SCIENTIFIC OVERVIEW AND DISCUSSION

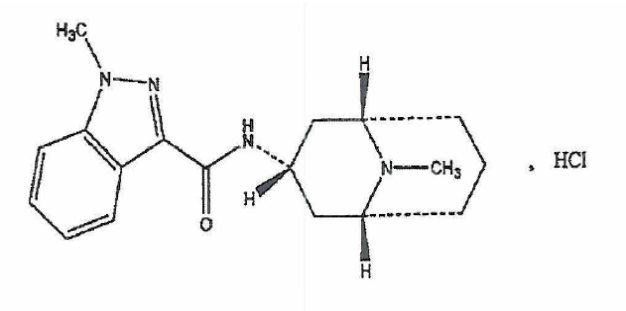
III.1 QUALITY ASPECTS

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.

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, 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 packs 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 3 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. Do not store above 25°C.”

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 25°C in normal indoor illumination protected from direct sunlight. From a microbiological point of view, the product should be used immediately. If to be stored, the dilutions should be prepared under appropriate 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

The pharmacological, pharmacokinetic and toxicological properties of granisetron hydrochloride are well-known. As granisetron hydrochloride is a well-known active substance, no further studies are required and the applicant has provided none.

A preclinical overview, based on a literature review, has been written by an appropriately qualified person and is a suitable summary of the preclinical aspects of the dossier.

The summary of product charateristics is satisfactory from a preclinical viewpoint.

The grant of a marketing authorisation is recommended.

III.3 CLINICAL ASPECTS

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

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 injection or 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 product.

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 or 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 or 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 or 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