Safeguarding public health

MHRA

Public Assessment Report

Granisetron 3mg/3ml Concentrate for Solution for Infusion

PL 15773/0516

Medicines and Healthcare products Regulatory Agency

GRANISETRON 3MG/3ML CONCENTRATE FOR SOLUTION FOR INFUSION

PL 15773/0516

UKPAR

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GRANISETRON 3MG/3ML CONCENTRATE FOR SOLUTION FOR INFUSION

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LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) has granted Ratiopharm GmbH a Marketing Authorisation (licence) for the medicinal product Granisetron 3mg/3ml Concentrate for Solution for Infusion (PL 15773/0516). This is a prescription only medicine [POM] used to prevent or treat nausea (feeling sick) and vomiting (being sick) caused by chemotherapy.

This product contains the active substance granisetron hydrochloride which acts on pathways known as 5-hydroxytryptamine ($5\text{-}HT_3$) receptors to prevent or treat the nausea and vomiting arising from chemotherapy.

The clinical data presented to the MHRA, before licensing, demonstrated that Granisetron 3mg/3ml Concentrate for Solution for Infusion is essentially similar or equivalent to the approved product, Kytril Infusion 3mg/3ml, and as such can be used interchangeably.

No new or unexpected safety concerns arose from this application and it was decided that the benefits of using Granisetron 3mg/3ml Concentrate for Solution for Infusion outweigh the risks, hence a Marketing Authorisation has been granted.

GRANISETRON 3MG/3ML CONCENTRATE FOR SOLUTION FOR INFUSION

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SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy the UK granted a Marketing Authorisation for the medicinal product Granisetron 3mg/3ml Concentrate for Solution for Infusion (PL 15773/0516) to Ratiopharm GmbH on 30 June 2006. Granisetron 3mg/3ml Concentrate for Solution for Infusion is a prescription only medicine.

The application was submitted as an abridged application according to Article 10.1(a)(iii) of Directive 2001/83/EC, claiming essential similarity to Kytril Infusion 3mg/3ml, which was first authorised in the UK on 14 November 1991.

This product contains the active ingredient granisetron hydrochloride and is indicated for the prevention or treatment of nausea and vomiting induced by cytostatic therapy.

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

PHARMACEUTICAL ASSESSMENT

LICENCE NO:	**PL 15773/0516**
PROPRIETARY NAME:	**Granisetron 3mg/3ml Concentrate for Solution for Infusion**
ACTIVE(S):	**Granisetron hydrochloride**
COMPANY NAME:	**Ratiopharm GmBH**
E.C. ARTICLE:	**10.1(a)(iii)**
LEGAL STATUS:	**POM**

REQUESTS FOR INSPECTION ACTION PRIOR TO AUTHORISATION

The finished product manufacturing site has been inspected by the MHRA and a GMP certificate has also been provided. The batch release site is Jenson Pharmaceutical Services Limited, UK.

INTRODUCTION

This is a national standard abridged application submitted under article 10.1(a)(iii) of Directive 2001/83/EC, cross-referring to the existing Kytril Infusion 3mg/3ml (Roche Products Ltd, PL 00031/0594, previously PL 10592/0003, granted in the UK on 14 November 1991).

Use

A selective 5-hydroxytriptamine (5-HT_3) receptor antagonist available for intravenous administration to prevent or treat cytotoxic therapy induced emesis.

DRUG SUBSTANCE

General information

The applicant refers to a previously assessed and approved drug master file. This is acceptable. Full testing is performed by the finished product manufacturer.

DRUG PRODUCT

Description and composition of the drug product

Ingredient	Function	Reference standard
Granisetron (as Granisetron hydrochloride)	Active ingredient	HSE
Sodium chloride	Osmotic agent	Ph.Eur.
Water for injection	Vehicle	Ph.Eur.

Manufacture

The proposed product is sterilised using a terminal sterilisation method. The method of manufacture has been provided for a commercial batch size.

Process validation or evaluation

A process validation study was performed on three commercial batches of proposed drug product using the proposed drug substance source and manufactured at the proposed site.

Control of excipients

Sodium chloride and water for injection are compliant with Ph.Eur., as supported by Certificates of Analysis.

Excipients of human or animal origin

No excipient used is of animal origin. The applicant has provided statements from the suppliers of both excipients confirming that there are no TSE concerns.

Control of drug product

A suitable finished product specification for Granisetron 3mg/3ml Concentrate for Solution for Infusion at release and shelf life has been provided.

Batch analysis data has been presented for 3 commercial scale batches manufactured at the proposed site and using the proposed drug substance source and these are well within specifications.

Suitability of the BP monograph (if applicable)

No BP monograph exists for the finished product.

Reference standards or materials

Certificates of Analysis have been provided for the reference standards of the drug substance and all impurities identified.

Container closure system

The product is presented in 3ml colourless Type I, glass ampoules with a blue and white colour ring identification.

Satisfactory specifications have been provided for the ampoules, and these are compliant with the requirements of the Ph.Eur. for glass containers for pharmaceutical use. Satisfactory Certificates of Analysis have been provided.

Stability

Three commercial scale batches of Granisetron 3mg/3ml Concentrate for Solution for Infusion ampoules presented in batch analysis have been tested for stability. Stability testing is performed in line with ICH guidelines at real time and accelerated conditions. The stability protocol shows testing intervals up to 36 months.

Analytical methods used for stability testing are the same as those used in the drug product specification.

All batches are within specification.

Bioequivalence/Bioavailability

Bioequivalence studies are not necessary to support this application, as the product is an aqueous solution.

Essential similarity

This has been shown.

FACILITIES AND EQUIPMENT

The finished product manufacturing site has been adequately described and a site diagram of the sterile production area has been provided.

PROCESS VALIDATION SCHEME FOR THE DRUG PRODUCT

The manufacturing process has been validated at the proposed manufacturing batch scale.

TSE ISSUES

A statement has been provided by the finished product manufacturer confirming that no intermediates and/or auxiliary agents of animal origin are used in the manufacture of this product.

NAME AND APPEARANCE

The proposed name is acceptable.

SUMMARY OF PRODUCT CHARACTERISTICS
PATIENT INFORMATION LEAFLET
LABELLING

Satisfactory.

ASSESSOR'S OVERALL CONCLUSIONS

Marketing Authorisation may be granted.

PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with this application and none are required.

CLINICAL ASSESSMENT

LICENCE NO:	**PL 15773/0516**
PROPRIETARY NAME:	**Granisetron 3mg/3ml Concentrate for Solution for Infusion**
ACTIVE(S):	**Granisetron hydrochloride**
COMPANY NAME:	**Ratiopharm GmBH**
E.C. ARTICLE:	**10.1(a)(iii)**
LEGAL STATUS:	**POM**

INTRODUCTION

This is a mainstream, national, abridged, standard licensing application submitted under Article 10.1(a)(iii) of Directive 2001/83/EC. The applicant is claiming essential similarity to Kytril Infusion 3mg/3ml (Roche Products Ltd, PL 00031/0594, previously PL 10592/0003, granted in the UK on 14 November 1991).

BACKGROUND

Granisetron is an anti-emetic agent. It belongs to a class of specific $5HT_3$ antagonists which block $5HT_3$ receptors in the gastrointestinal tract and in the central nerveous system. These drugs are of value in the management of nausea and vomiting in patients receiving cytotoxics and in postoperative nausea and vomiting.

INDICATIONS

Granisetron is indicated for the prevention or treatment of nausea and vomiting induced by cytostatic therapy.

This is consistent with the reference product's indications.

DOSE AND DOSE SCHEDULE

These are in line with those of the reference product.

TOXICOLOGY

No new data are provided or needed. However, the applicant has submitted a Preclinical Expert summary.

CLINICAL PHARMACOLOGY

Bioequivalence

No comparative pharmacokinetic data have been submitted and none are required. The applicant has provided an adequate justification for the exemption of a bioequivalence study.

EFFICACY

No new data required. However, the applicant has submitted copies of several publications with a summary review of the literature confirming the effectiveness of granisetron.

SAFETY

No new data needed. However, the applicant has provided several copies of publications with a safety review from the literature. No new safety issues have been detected.

EXPERT REPORT

A satisfactory brief clinical expert report/overview has been submitted, with an appropriate CV.

SUMMARY OF PRODUCT CHARACTERISTICS
PATIENT INFORMATION LEAFLET
LABELLING

These are satisfactory.

DISCUSSION

Specific $5HT_3$ antagonists, including granisetron, which block $5HT_3$ receptors in the gastrointestinal tract and in the central nervous system have been available in the EU for over 10 years. Their use is well established with recognised efficacy and acceptable safety.

CONCLUSION

Marketing authorisation may be granted on medical grounds.

OVERALL CONCLUSION AND RISK-BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Granisetron 3mg/3ml Concentrate for Solution for 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.

PRECLINICAL

No new preclinical data were submitted and none are required for applications of this type.

EFFICACY

No clinical pharmacology data or clinical trials data have been submitted to directly support the claim of essential similarity of the proposed product to the proprietary product Kytril Infusion 3mg/3ml (PL 00031/0594). This is acceptable as the formulations are similar and the same routes of administration are proposed.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with those of Kytril Infusion 3mg/3ml.

RISK-BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with granisetron is considered to have demonstrated the therapeutic value of the compound. The risk-benefit assessment is therefore considered to be favourable.

GRANISETRON 3MG/3ML CONCENTRATE FOR SOLUTION FOR INFUSION

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STEPS TAKEN FOR ASSESSMENT

1	The MHRA received the marketing authorisation application for Granisetron 3mg/3ml Concentrate for Solution for Infusion on 22 December 2004.
2	The MHRA's assessment of the submitted clinical data was completed on 14 July 2005.
3	Further information (clinical) was requested from the company on 14 July 2005.
4	The MHRA's assessment of the submitted quality data was completed on 23 September 2005.
5	Further information (quality) was requested from the company in a letter dated 28 September 2005.
6	The applicant's response to further information request (quality) was sent in a letter dated 19 December 2005.
7	Further information (quality) was requested from the company in a letter dated 27 April 2006.
8	The applicant's response to further information request (quality) was sent on 1 June 2006.
9	The MHRA completed its assessment of the application on 29 June 2006.
10	The application was determined on 30 June 2006.

GRANISETRON 3MG/3ML CONCENTRATE FOR SOLUTION FOR INFUSION

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STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Granisetron 3 mg/3 ml Concentrate for Solution for Infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 3 ml contains 3.0 mg granisetron (as hydrochloride).

For a full list of excipients, section see 6.1.

3. PHARMACEUTICAL FORM

A glass ampoule containing a sterile, clear colourless solution. The content of the 3 ml ampoule allows withdrawal of 3 ml.

Concentrate for solution for infusion or bolus injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Granisetron 3 mg/3 ml Concentrate for Solution for Infusion is indicated for the prevention or treatment of nausea and vomiting induced by cytostatic therapy.

4.2 Posology and method of administration

Cytostatic therapy

Granisetron 3 mg/3 ml Concentrate for Solution for Infusion is for intravenous administration only.

Adults

The product should be administered either in 15 ml infusion fluid as an intravenous bolus over not less than 30 seconds or diluted in 20 to 50 ml of infusion fluid and administered over five minutes.

Prevention: In clinical trials, the majority of patients have required only a single dose of granisetron to control nausea and vomiting over 24 hours. Up to two additional doses of 3 mg of granisetron may be administered within a 24 hour period. There is clinical experience in patients receiving daily administration for up to five

consecutive days in one course of therapy. Prophylactic administration 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 dose: Up to three doses of 3 mg of 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 dexamethasone: The efficacy of granisetron may be enhanced by the addition of dexamethasone.

Children

Prevention: A single dose of 40 µg/kg bodyweight (up to 3 mg) should be administered as an intravenous infusion, diluted in 10 to 30 ml infusion fluid 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 40 µg/kg bodyweight (up to 3 mg) may be administered within a 24-hour period if required. This additional dose should be administered at least 10 minutes apart from the initial infusion.

Renally Impaired

No special requirements apply.

Hepatically Impaired

No special requirements apply.

4.3 Contraindications

Hypersensitivity to granisetron or related substances.

4.4 Special warnings and precautions for use

As granisetron may reduce lower bowel motility, patients with signs of sub-acute intestinal obstruction should be monitored following administration of Granisetron 3 mg/3 ml Concentrate for Solution for Infusion.

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

4.5 Interaction with other medicinal products and other forms of interaction

In studies in healthy subjects, no evidence of any interaction has been indicated between granisetron and cimetidine or lorazepam. No evidence of drug interactions has been observed in clinical studies conducted.

No specific interaction studies have been conducted in anaesthetised patients but granisetron has been safely administered with commonly used anaesthetic and analgesic agents. In addition, in vitro human microsomal studies have shown that the cytochrome P450 sub family 3A4 (involved in the metabolism of some of the main narcotic analgesic agents) is not modified by granisetron.

4.6 Pregnancy and lactation

Pregnancy
Whilst animal studies have shown no teratogenic effects, there is no experience of granisetron in human pregnancy. Therefore, Granisetron 3 mg/3 ml Concentrate for Solution for Infusion should not be administered to women who are pregnant unless there are compelling clinical reasons.

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

4.7 Effects on ability to drive and use machines

None known.

4.8 Undesirable effects

Granisetron has been generally well tolerated in human studies. As reported with other drugs of this class, headache and constipation have been the most frequently noted adverse events but the majority have been mild or moderate in nature. Rare cases of hypersensitivity reaction, occasionally severe (e.g. anaphylaxis) have been reported. Other allergic reactions including minor skin rashes have also been reported. In clinical trials, transient increases in hepatic transaminases, generally within the normal range have been seen.

4.9 Overdose

There is no specific antidote for granisetron. In the case of overdosage, symptomatic treatment should be given. One patient has received 30 mg of granisetron

intravenously. The patient reported a slight headache but no other sequelae were observed.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: A 04 AA 02. Serotonin (5HT3) antagonists.

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

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

Granisetron is effective, intravenously, in the prevention and treatment of post-operative nausea and vomiting.

5.2 Pharmacokinetic properties

General Characteristics
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 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 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

Data from two-year carcinogenicity studies have shown an increase in hepatocellular carcinoma and/or adenoma in rats and mice of both sexes given 50 mg/kg (rat dosage reduced to 25 mg/kg/day at week 59). Increases in hepatocellular neoplasia were also detected at 5 mg/kg in male rats. In both species, drug-induced effects (hepatocellular neoplasia) were not observed in the low-dose group (1 mg/kg).

In several in vitro and in vivo assays, granisetron was shown to be non-genotoxic in mammalian cells.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Water for injection

6.2 Incompatibilities

As a general precaution, Granisetron 3 mg/3 ml Concentrate for Solution for Infusion should not be mixed in solution with other drugs. Prophylactic administration of Granisetron 3 mg/3 ml Concentrate for Solution for Infusion should be completed prior to the start of cytostatic therapy.

6.3 Shelf life

Unopened shelf-life: 3 years

Opened shelf-life: 24 hours

6.4 Special precautions for storage.

Keep ampoules in the outer carton. Do not freeze.

6.5 Nature and contents of container

Granisetron 3 mg/3 ml Concentrate for Solution for Infusion is supplied in clear glass ampoules supplied in packs of one or five ampoules in an outer carton.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Preparing the infusion

Adults: To prepare the dose of 3 mg, 3 ml is withdrawn from the ampoule and diluted either to 15 ml with 0.9% w/v Sodium Chloride Injection (for bolus administration) or in infusion solution to a total volume of 20 to 50 ml in any of the following solutions:

0.9% w/v Sodium Chloride Injection
0.18% w/v Sodium Chloride and 4 % w/v Glucose Injection
5% w/v Glucose Injection
Hartmann's Solution for Injection
Sodium Lactate Injection
10% Mannitol Injection

No other diluents should be used.

Children: To prepare the dose of 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.

Ideally, intravenous infusions of Granisetron 3 mg/3 ml Concentrate for Solution for Infusion should be prepared at the time of administration. After dilution (see above), the shelf-life is 24 hours when stored at ambient temperature 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.

As a general precaution, Granisetron 3 mg/ml concentrate for solution for infusion should not be mixed in solution with other drugs.

7. MARKETING AUTHORISATION HOLDER

ratiopharm GmbH
Graf-Arco-Strasse 3
D-89070 Ulm
Germany

8. MARKETING AUTHORISATION NUMBER(S)

PL 15773/0516

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

30/06/2006

10 DATE OF REVISION OF THE TEXT

30/06/2006

Patient Information Leaflet

GRANISETRON 3MG/3ML CONCENTRATE FOR SOLUTION FOR INFUSION

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PATIENT INFORMATION LEAFLET

Read this entire leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should NOT pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:

Granisetron 3 mg/3 ml Concentrate for Solution for Infusion

(Granisetron hydrochloride)

1. What is in *Granisetron 3mg/3ml Concentrate for Solution for Infusion*?

The name of this medicine is *Granisetron 3mg/3ml Concentrate for Solution for Infusion*.

Granisetron 3mg/3ml Concentrate for Solution for Infusion contain the active ingredient granisetron. Each 3 ml ampoule contains 3 mg granisetron as the hydrochloride in a 3 ml sterile solution.

They also contain the following inactive ingredients: sodium chloride and water. Each 1 ml contains 3.54 mg of sodium.

The 3 ml ampoules are available in packs of one and five ampoules.*
**Not all pack sizes may be marketed.*

Marketing Authorisation Holder:
ratiopharm GmbH, Graf-Arco-Str. 3, D-89079 Ulm, Germany.

Manufacturer:
Jenson Pharmaceutical Services Limited, Carradine House, 237 Regents Park Road, London N3 3LF, UK.

2. What is your medicine 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 nausea (feeling sick) and vomiting (being sick).

This medicine can stop you from feeling or being sick, and is especially useful when you need to have medical treatment that may cause you to feel or be sick.
In children, *Granisetron 3mg/3ml Concentrate for Solution for Infusion* are used to stop them from feeling or being sick after certain types of treatment, for example, chemotherapy or radiotherapy.

Granisetron 3mg/3ml Concentrate for Solution for Infusion is intended for hospital use only.

3. Before you have *Granisetron 3mg/3ml Concentrate for Solution for Infusion*

Granisetron is not suitable for everyone. If you answer **yes** to any of the following questions, tell your doctor or nurse before you are given your medicine. You may need to be given another medicine instead.

- Are you allergic to granisetron or any related drugs (such as ondansetron)?
- Have you been told by a doctor that your bowels don't work properly?
- Do you have any pain in your abdomen (tummy) or does your abdomen feel distended or swollen?
- Are you pregnant or do you think you may be?
- Are you breast-feeding?
- Do you have severe constipation?

You should not be given this medicine if you are pregnant or are breast feeding unless your doctor has specifically recommended it.

4. How *Granisetron 3mg/3ml Concentrate for Solution for Infusion* is given

Granisetron will be given to you by your doctor or nurse:
- In **adults** as a slow intravenous injection (into a vein) in 15 ml in fusion fluid given over 30 seconds or diluted in 20 to 50ml of in fusion fluid given over 5 minutes.
- In **children** as an intravenous infusion diluted in 10 to 30 ml of fluid given over five minutes.

Granisetron is usually given before the medication that is likely to make you feel sick, although it can be given afterwards to stop any sickness you may be having.

The usual dosages are:
- In adults the same dose should be used for treatment as prevention. Additional doses should be administered at least 10 minutes apart. Upto 3 doses of granisetron may be administered within a 24-hour period. No more than 9 mg should be given in one day.
- In children 40 micrograms for each kilogram (kg) of body weight (up to 3 mg) to prevent sickness before chemotherapy or radiotherapy. For example a 20 kg child would have 0.8 mg of Granisetron. The same dose may be given after treatment to stop sickness. No more than two doses should be given within 24 hours.

Since you will be given the injection by a doctor or nurse it is unlikely that you will be given too much or that you will miss a dose. However, if you are worried talk to your doctor or nurse.

GRANISETRON 3MG/3ML CONCENTRATE FOR SOLUTION FOR INFUSION

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5. Possible side effects
Like all medicines, *Granisetron 3mg/3ml Concentrate for Solution for Infusion* can have side effects in some patients, but most of these are not serious.

Some patients may experience headache or constipation.

Occasionally, allergic reactions also occur. Tell your doctor if you get a rash or start to itch. You should tell your doctor straight away if you become short of breath or get a swollen face. These reactions are rare but need urgent medical treatment.

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 you experience any of these side effects or any others not mentioned in this leaflet, please talk to your doctor or nurse.

6. Storing your *Granisetron 3mg/3ml Concentrate for Solution for Infusion*
Keep the ampoules in the outer carton. Do not freeze. There is an expiry date on the carton and ampoule label, the doctor or nurse will check that this date has not been passed.

Keep *Granisetron 3mg/3ml Concentrate for Solution for Infusion* out of the reach and sight of children

Date of leaflet preparation: October 2005

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

Instructions for preparing the infusion:
Adults: To prepare the dose of 3 mg, 3 ml is withdrawn from the ampoule and diluted either to 15 ml with 0.9% w/v Sodium Chloride Injection (for bolus administration) or in infusion solution to a total volume of 20 to 50 ml in any of the following solutions:

0.9% w/v Sodium Chloride Injection
0.18% w/v Sodium Chloride and 4 % w/v Glucose Injection
5% w/v Glucose Injection
Hartmann's Solution for Injection
Sodium Lactate Injection
10% Mannitol Injection

No other diluents should be used.

Children: To prepare the dose of 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.

No other diluents should be used.

Ideally, intravenous infusions of *Granisetron 3mg/3ml Concentrate for Solution for Infusion* should be prepared at the time of administration. After dilution (see above), the shelf-life is 24 hours when stored at ambient temperature 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. As a general precaution, Granisetron 3mg/3ml Concentrate for Solution for Infusion should not be mixed in solution with other drugs.

ratiopharm

Labels/Packaging

GRANISETRON 3MG/3ML CONCENTRATE FOR SOLUTION FOR INFUSION

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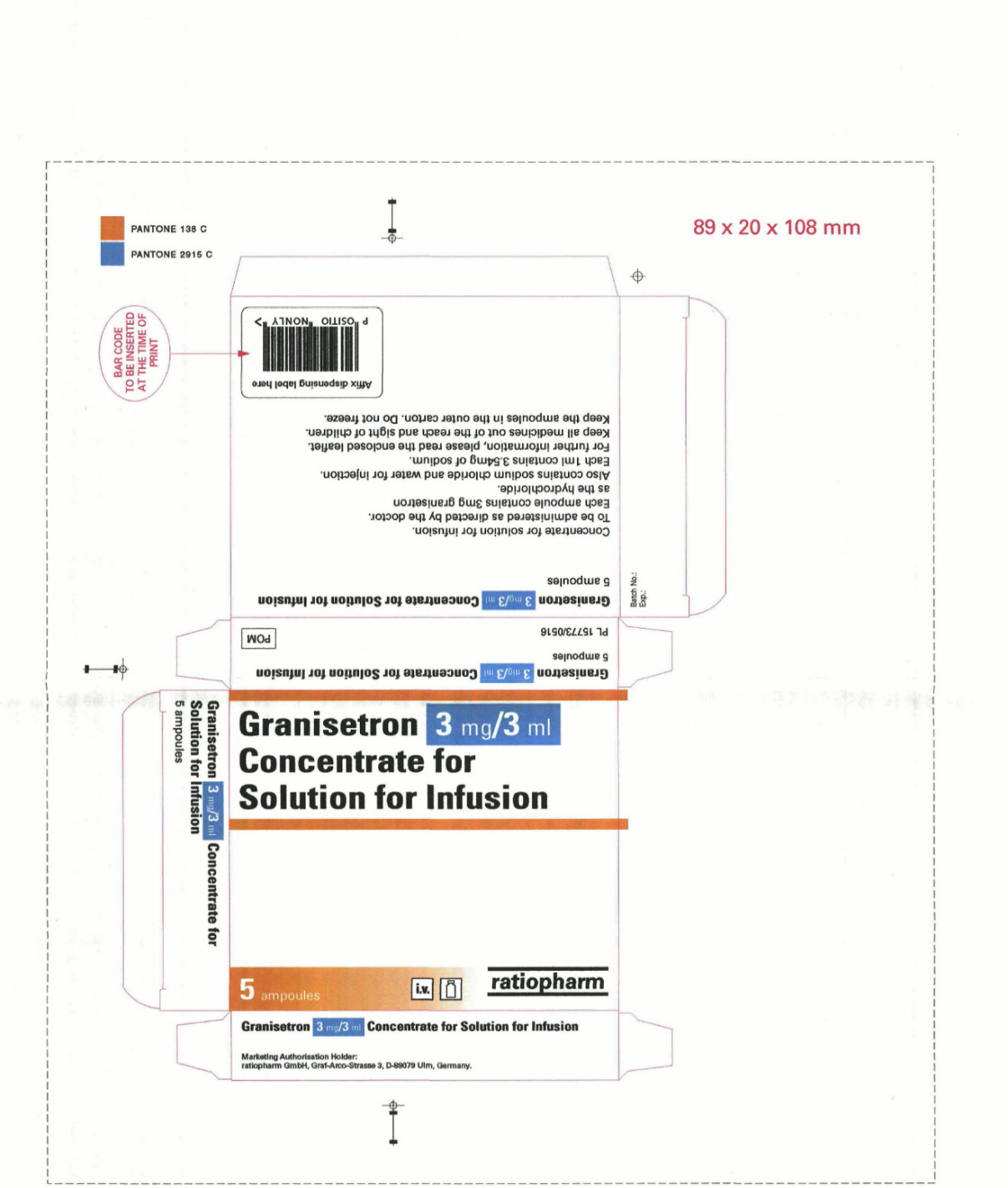

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