

**GRANISETRON 1 MG TABLETS
(GRANISETRON HYDROCHLORIDE)
PL 15773/0514**

**GRANISETRON 2 MG TABLETS
(GRANISETRON HYDROCHLORIDE)
PL 15773/0515**

UKPAR

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LAY SUMMARY

The MHRA granted Ratiopharm GMBH Marketing Authorisations (licences) for the medicinal products Granisetron 1mg Tablets (PL 15773/0514) and Granisetron 2mg Tablets (PL 15773/0515) on 6th June 2006. These prescription only medicines (POM) are used for the prevention of nausea and vomiting caused by cancer chemotherapy and radiotherapy.

Granisetron Tablets contain the active ingredient granisetron hydrochloride, which is an anti-emetic, used to prevent nausea and vomiting.

The data presented to the MHRA, pre licensing, demonstrated that Granisetron 1mg & 2mg Tablets are equivalent to the approved products, Kytril 1mg and 2mg Tablets. Granisetron Tablets can therefore be used interchangeably with Kytril Tablets.

No new or unexpected safety concerns arose from these applications. It was, therefore, judged that the benefits of taking Granisetron Tablets outweigh the risks. Hence, Marketing Authorisations have been granted.

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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 marketing authorisations for the medicinal products Granisetron 1mg Tablets (PL 15773/0514) and Granisetron 2mg Tablets (PL 15773/0515) to Ratiopharm GMBH on 6th June 2006. The products are prescription only medicines.

The applications were submitted as abridged applications according to article 10.1 [formerly article 10.1(a)(iii)] of Directive 2001/83/EC, claiming essential similarity to the original products Kytril 1mg & 2mg Tablets.

The products contain the active ingredient granisetron hydrochloride and are indicated for the management of nausea and vomiting induced by cytostatic therapy.

Granisetron is a potent anti-emetic and highly selective antagonist of 5-hydroxytryptamine (5-HT₃) receptors. Granisetron is effective as an oral prophylactic in abolishing the retching and vomiting evoked by cytostatic therapy.

PHARMACEUTICAL ASSESSMENT

1. GMP STATUS

The primary manufacturing site for manufacture and assembly in Israel has been inspected by the Danish Medicines Agency in November 2003.

Jenson Pharmaceutical Services Ltd, UK is responsible for batch release in the EEA. The batch control site has been specified and a current manufacturing licence supplied.

2. INTRODUCTION

These national abridged applications for Granisetron (hydrochloride) tablets are made under EC Article 10.1 [formerly 10.1(a)(iii)] of the Directive 2001/83/EC claiming essential similarity to the originator product by Roche Products Ltd., Kytril 1mg and 2mg Tablets (PL 00031/0591-2 granted 15th September 2001, original licenses PL 10592/0032 Kytril tablets 1mg, granted 04th January 1994, expired 14-12-2001 and PL 10592/0067 Kytril Tablets 2mg, granted 26th February 1996, expired 14-12-2001). Granisetron hydrochloride tablets are indicated for the prevention of nausea and vomiting induced by cytostatic therapy.

MODULE 3

3.2.S. DRUG SUBSTANCE

The Active Substance Manufacturer has submitted a Drug Master File, which has been assessed and approved in relation to another application.

Granisetron hydrochloride is freely soluble in water (>1 in 10) and slightly soluble in ethanol (about 1 in 120).

3.2.P DRUG PRODUCT

3.2.P.1 Qualitative Composition

Ingredient	Reference to Standard
Granisetron hydrochloride	PhEur
Lactose monohydrate	PhEur
Microcrystalline cellulose	PhEur
Hydroxypropylmethyl cellulose	PhEur
Sodium starch glycollate	PhEur
Magnesium stearate	PhEur
Opadry YS-1R-7003	HSE
Purified water*	PhEur

*Removed during the process.

The 1 and 2mg tablets composition are quantitatively and qualitatively the same and their compositions are linear. The two strengths are differentiated by tablet markings (GS and GS2).

3.2.P.2 Pharmaceutical development

The products were initially developed to be equivalent to the brand leader sourced from Israel, Kytril, in compliance with Israeli regulations. Additional development studies were performed on the proposed product in order to expand the marketing of the product to the European Union.

Qualitative justification of the excipients selected is provided. Three batches of each strength of tablet were manufactured in 2003. In vitro comparative testing (assay, related substances and dissolution) between the proposed and brand leader products sourced from the UK, France, Netherlands and Germany is presented and is comparable. The dissolution method was developed through dissolution studies of the same batch using different media according to PhEur, and different apparatus paddle and stirring speeds, showing that these parameters do not affect the rapid dissolution of the product. As the drug is water soluble, this is acceptable.

Manufacturing process development is not presented. It is stated that the manufacturer had previous experience with this formulation and the repeatability of the process was re-tested through process qualification. Optimisation studies on some parameters have been presented.

The finished product manufacturer chose PVC/PVDC/aluminium blisters for granisetron tablets and has amassed three years real time stability data on the tablet formulation in this packaging, therefore no further pack compatibility studies were deemed necessary.

Bioequivalence Studies

See Clinical Assessment for details of bioequivalence studies.

3.2.P.3 Manufacture

Three 'pilot' scale batches of 1mg tablets, and three commercial scale batches of 2mg tablets were manufactured. The applicant justifies the intended commercial scale of tablets for the 2mg product due to market share reasons. The applicant states that the pilot batch formula may be adjusted for the 1mg tablet strength following appropriate validation.

An outline of the manufacturing process and flow diagram is provided in the dossier. The manufacturing process is a conventional aqueous wet granulation process. Frequency and methods of testing during in-process testing is specified.

The applicant has committed to performing process validation on the first three commercial batches produced.

Internal procedures of the finished product manufacturer includes stability testing of the bulk packed tablets to derive accepted holding time and transportation studies to test the physical and chemical stability of the bulk and packaged tablets. These tests will be performed on the first commercial batch to be manufactured. The finished product manufacturer previously performed bulk stability testing for the product marketed in Israel and stability data for Granisetron 1mg

Tablets packed in bulk have been provided. The holding time proposed is 6 months. This is supported by the stability data provided.

Uniformity of content is adequately controlled.

Confirmation has been provided that no batches will be manufactured for sale which exceed the proposed manufacturing batch size, unless supported by suitable manufacturing data and variation of the licence.

3.2.P.4 Control of excipients

All excipients used are Ph Eur grade material. Certificates of analysis from the suppliers and drug product manufacturer's acceptance specifications have been provided for all excipients.

Excipients of human or animal origin

An assurance has been provided from the named lactose supplier that it is sourced exclusively from healthy animals in the same conditions as for milk sourced for human consumption, and that no other products of animal origin, with the exception of calf rennet, are employed in its manufacture. Vegetable grade magnesium stearate is from a named source.

A commitment has been provided that all excipients will comply with the current edition of the European Pharmacopoeia.

3.2.P.5 Control of drug product

A comprehensive specification is provided including tests for assay, identification of granisetron by HPLC and UV, identification of titanium dioxide by TLC, appearance, uniformity of mass, average mass, hardness, loss on drying, disintegration, dissolution, related substances, and microbial controls.

Related substances limits are in line with ICH guidelines and the drug substance specification as well as batch data.

All analytical test methods have been provided and validated.

Forced degradation studies were performed and all samples fell within finished product specifications with the exception of assay on heat treated sample, which may be justified by a loss of moisture of the sample, indicating that the HPLC method used is stability indicating.

Batch analysis data have been presented, for each tablet strength, manufactured using the proposed drug substance source at the proposed manufacturing site, in 2003. Results are satisfactory and within limits. Adequate justification for specifications has been provided.

Microbiological testing is adequate.

3.2.P.6 Reference Standard

Reference standards obtained for granisetron hydrochloride drug substance and all impurities used for the quantitation of granisetron and impurities have been provided. Certificates of analysis for all of the above are provided.

3.2.P.7 Container closure system

The tablets are packaged in press-through blister strips of opaque PVC/PVdC and aluminium.

Satisfactory supplier and finished product manufacturer's acceptance specifications and test procedures have been provided. An IR spectrum for aluminium has been provided. Confirmation has been provided that all packaging that comes into direct contact with the drug product complies with European Directive 90/128/EEC with respect to their suitability for contact with food.

3.2.P.8 Stability

Test batches were placed on stability studies, in the proposed packaging intended for marketing. Storage is under long term and accelerated ICH conditions. Stability protocols have been provided.

Parameters monitored during stability of the product include appearance, uniformity of mass, average tablet weight, assay, related substances, dissolution, hardness, loss on drying, microbial contamination. Specifications are the same as those at release. All results fall within specifications.

Photostability testing results have also been provided and show that Granisetron 1mg and 2mg tablets are stable also under extreme conditions. Assay and Impurities levels remain within specification and extent of degradation is low.

The applicant proposes a shelf-life of 36 months and satisfactory data has been submitted to support this shelf life. A commitment to placing the first three commercial size batches on stability has been provided.

MODULE 1

MAA forms, Summary of Product Characteristics, Labelling & Package Leaflet

The MAA forms, SPC, labelling and package leaflet are satisfactory

MODULE 2

2.3 Quality Overall Summary

The quality overall summary is an accurate reflection of the data provided.

PHARMACEUTICAL RECOMMENDATION

Marketing Authorisations may be granted.

PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with these applications and none are required for applications of this type.

CLINICAL ASSESSMENT

1. INTRODUCTION

This is a mainstream, national, abridged, standard licensing application submitted under article 10.1 [formerly 10.1a(iii)] of the Directive 2001/83/EC. The applicant is claiming essential similarity to Kytril 1mg Tablet (Roche Products Ltd –PL 00031/0591), UK licence was granted in January 1994.

2. BACKGROUND

Granisetron is an anti-emetic agent. It belongs to a class of specific 5HT₃ antagonists which block 5HT₃ receptors in the gastro-intestinal tract and in the central nervous system. These drugs are of value in the management of nausea and vomiting in patients receiving cytotoxics and in postoperative nausea and vomiting.

3. INDICATIONS

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

Assessor's Comment

These are consistent with those of the reference product license.

4. DOSE & DOSE SCHEDULE

These are in line with those of the reference product license.

5. TOXICOLOGY

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

6. CLINICAL PHARMACOLOGY

6.1 Pharmacodynamics

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.

6.2. Pharmacokinetics

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.

6.3 Bioequivalence

Granisetron 1mg Tablets

The applicant has submitted a comparative bioavailability study involving 66 subjects. This was a two way balanced, randomised crossover single dose study comparing the bioavailability of Granisetron 1mg tablet and Kytril™ 1mg (Roche, UK). Blood samples were taken at frequent intervals up to 48 hours post dosing. There was a washout period of 14 days. Granisetron was assayed using a validated method. Statistical evaluation was performed using standard procedures. The main pharmacokinetic parameters are summarised in the table below.

Pharmacokinetic Variables For Granisetron KYTRIL™ (Roche) and Granisetron 1mg Tablets)

VARIABLE	KYTRIL	GRANISETRON	90% CI
C _{max} (ng/ml)	5.6	5.79	97.8-109
T _{max} (h)	1.5	1.5	-
AUC _{0-t} (ng.h/ml)	47.9	51.2	97.7-117
AUC _{0-∞} (ng.h/ml)	50.2	53.6	97.8-117
T _½ (h)	6.14	6.21	95.9-107

C.I.: Confidence Interval (%)

Pharmacokinetic Variables For 7-Hydroxy Granisetron (KYTRIL™ (Roche) and Granisetron 1mg Tablets)

VARIABLE	KYTRIL	GRANISETRON	90% CI
C _{max} (ng/ml)	0.59	0.6	90.5-116
T _{max} (h)	1.5	1.5	-
AUC _{0-t} (ng.h/ml)	10.8	10.9	94.8-107
AUC _{0-∞} (ng.h/ml)	12.3	12.4	96.0-106
T _½ (h)	13.9	13.7	93.8-104

C.I.: Confidence Interval (%)

The results show that the 90% confidence intervals of the relative C_{max}, AUC_{0-t}, AUC_{0-∞} and C_{max} of the Test to the Reference formulation were all within the acceptable range for both Granisetron and its metabolite 7-Hydroxy Granisetron.

Sixty-one adverse events were reported. Headache (30) was the most common adverse event. All events were of mild or moderate severity. Other reported events included nausea, stomach-aches and abdominal cramps. There was no significant difference between adverse event profile of the test and reference products. No serious adverse events were reported.

Granisetron 2mg Tablets

This was a single-dose, randomized, two-period, two sequence cross-over study. The 40 study subjects received an oral dose of one 2mg tablet of granisetron as test or as reference formulation.

For the comparison of the extent and rate of absorption of the two investigated formulations the 90% confidence intervals were calculated for the log-transformed parameters. AUC_{0-∞}, AUC_{0-t}, C_{max}, and C_{max} were treated as primary metrics of bioequivalence.

The main pharmacokinetic parameters are summarised in tables below.

Pharmacokinetic Variables For Granisetron KYTRIL™ (Roche) and Granisetron 2mg Tablets)

VARIABLE	KYTRIL	GRANISETRON	90% CI
C _{max} (ng/ml)	9.74	6.69	93.8 ; 105
T _{max} (h)	1.50	1.33	
AUC _{0-t} (ng.h/ml)	66.1	66.7	90.7 ; 112
AUC _{0-∞} (ng.h/ml)	69.5	70.7	91.9 ; 112
T _½ (h)	5.00	5.16	96.9 ; 110

Pharmacokinetic Variables For 7-Hydroxy Granisetron (KYTRIL™ (Roche) and Granisetron 2mg Tablets)

VARIABLE	KYTRIL	GRANISETRON	90% CI
C _{max} (ng/ml)	1.51	1.53	88.4 ; 115
T _{max} (h)	1.67	1.67	
AUC _{0-t} (ng.h/ml)	21.30	21.1	91.5 ; 107
AUC _{0-∞} (ng.h/ml)	24.50	24.4	93.8 ; 106

$T_{1/2}(h)$	11.90	11.7	93.4 ; 103
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C.I.: Confidence Interval (%)

The results show that the 90% confidence intervals of the relative C_{max} , AUC_{0-t} , $AUC_{0-\infty}$ and C_{max} of the Test to the Reference formulation were all within the acceptable range for both Granisetron and its metabolite 7-Hydroxy Granisetron.

No serious adverse events were reported during this study. No adverse events related to laboratory variable were reported.

Thirty-four adverse events were reported by twenty-six subjects. Headache was the predominant adverse event reported. Sixteen headaches were reported by fourteen subjects. Eleven of the sixteen headaches reported were assessed as possibly related to the study medication and the intensity was rated from "mild" to "moderate".

Eighteen adverse events other than headache were reported by 14 subjects. Of these the investigator considered seven not to be related, seven unlikely to be related three to be possible related to the study medication and one adverse event as not assessable.

7. EFFICACY

No new data are submitted or required.

8. SAFETY

No new data are provided or needed.

9. EXPERT REPORT

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

10. SUMMARY OF PRODUCT CHARACTERISTICS

The text of the proposed SPC is basically the same as that of the cross-referenced product.

11. PATIENT INFORMATION LEAFLET

This is satisfactory.

12. LABELLING

Full colour mock-ups have been provided and are satisfactory.

13. DISCUSSION

Specific 5HT₃ antagonists, including granisetron, which block 5HT₃ receptors in the gastrointestinal tract and in the central nervous system have been available in the EU for over ten years. Their use is well established with recognised efficacy and acceptable safety.

14. CONCLUSION

Marketing authorisations may be granted on medical grounds.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Granisetron 1mg and 2mg Tablets 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 have been supplied with these applications and none are required for applications of this type.

EFFICACY

Bioequivalence has been demonstrated between the applicant's Granisetron Tablets and the originator products, Kytril Tablets.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with that for Kytril Tablets.

RISK BENEFIT ASSESSMENT

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

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PL 15773/0515**

STEPS TAKEN FOR ASSESSMENT

1	The MHRA received the marketing authorisation application on 22/12/2004
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 19/01/2005
3	Following assessment of the application the MHRA requested further information relating to the dossier on 05/09/2005 and 02/03/2006.
4	The applicant responded to the MHRA's requests, providing further information relating to the dossier on 20/10/2005, 19/04/2006 and 11/05/2006.
5	The application was determined on 06/06/2006

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STEPS TAKEN AFTER ASSESSMENT

Date submitted	Application type	Scope	Outcome

**GRANISETRON 1 MG TABLETS
(GRANISETRON HYDROCHLORIDE)
PL 15773/0514**

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Granisetron 1 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 1 mg granisetron (as the hydrochloride).

Contains lactose. For a full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

White to off-white tablet embossed "GS" on one side and plain on the reverse

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Granisetron tablets are indicated for the prevention of nausea and vomiting induced by cytostatic therapy.

4.2 Posology and method of administration

Adults:

The dose of granisetron is 1 mg twice a day or 2 mg once a day during cytostatic therapy. The first dose of granisetron should be administered within one hour before the start of cytostatic therapy.

Concomitant use of dexamethasone: The efficacy of granisetron may be enhanced by the addition of dexamethasone.

Maximum Dose and Duration of Treatment:

Granisetron is also available as ampoules for intravenous administration. The maximum dose of granisetron administered orally and/or intravenously over 24 hours should not exceed 9 mg.

Children:

There is insufficient evidence on which to base appropriate dosage regimens for children under 12 years old. Granisetron tablets are therefore not recommended in this age group.

Elderly:

As recommended for adults.

Renally Impaired:

As recommended for adults.

Hepatically Impaired:

As recommended for adults.

4.3 Contraindications

Granisetron is contra-indicated in patients hypersensitive 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. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Studies in healthy subjects have shown no evidence of any interaction between granisetron and cimetidine or lorazepam. No evidence of drug interactions has been observed in clinical studies.

4.6 Pregnancy and lactation**Pregnancy:**

Animal studies have shown no teratogenic effects, but there is no reported experience of using 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.

4.7 Effects on ability to drive and use machines

There has been no evidence from human studies that granisetron has any adverse effect on alertness.

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 has 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 who received 30 mg of granisetron intravenously reported a slight headache but no other sequelae were observed.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiemetics and antinauseants
ATC Code: A04A

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

Granisetron is effective as an oral prophylactic in abolishing the retching and vomiting evoked by cytostatic therapy.

5.2 Pharmacokinetic properties

Absorption:

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

Distribution:

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

Biotransformation:

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 9 hours, with a wide inter-subject variability.

The pharmacokinetics of granisetron demonstrate no marked deviations from linear pharmacokinetics at oral doses up to 2.5-fold of the recommended clinical dose.

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 considered to be 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

Lactose Monohydrate
Cellulose Microcrystalline
Hypromellose
Sodium Starch Glycolate (type A)
Magnesium Stearate
Titanium Dioxide (E171)
Macrogol 400
Polysorbate 80

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

This product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/PVDC aluminium foil opaque blisters in a cardboard carton containing 1, 2, 4, 5, 6, 7, 10, 14, 20, 28, 30, 50, 90, 100, 150, 200, 250 and 500 tablets. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

PL 15773/0514

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

06/06/2006

10 DATE OF REVISION OF THE TEXT

06/06/2006

**GRANISETRON 2 MG TABLETS
(GRANISETRON HYDROCHLORIDE)
PL 15773/0515**

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Granisetron 2 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2 mg granisetron (as the hydrochloride).

Contains lactose. For a full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

White to off-white tablet embossed "GS2" on one side and plain on the reverse

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Granisetron tablets are indicated for the prevention of nausea and vomiting induced by cytostatic therapy.

4.2 Posology and method of administration

Adults:

The dose of granisetron is 1 mg twice a day or 2 mg once a day during cytostatic therapy. The first dose of granisetron should be administered within one hour before the start of cytostatic therapy.

Concomitant use of dexamethasone: The efficacy of granisetron may be enhanced by the addition of dexamethasone.

Maximum Dose and Duration of Treatment:

Granisetron is also available as ampoules for intravenous administration. The maximum dose of granisetron administered orally and/or intravenously over 24 hours should not exceed 9 mg.

Children:

There is insufficient evidence on which to base appropriate dosage regimens for children under 12 years old. Granisetron tablets are therefore not recommended in this age group.

Elderly:

As recommended for adults.

Renally Impaired:

As recommended for adults.

Hepatically Impaired:

As recommended for adults.

4.3 Contraindications

Granisetron is contra-indicated in patients hypersensitive 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. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Studies in healthy subjects have shown no evidence of any interaction between granisetron and cimetidine or lorazepam. No evidence of drug interactions has been observed in clinical studies.

4.6 Pregnancy and lactation

Pregnancy:

Animal studies have shown no teratogenic effects, but there is no reported experience of using 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.

4.7 Effects on ability to drive and use machines

There has been no evidence from human studies that granisetron has any adverse effect on alertness.

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 has 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 who received 30 mg of granisetron intravenously reported a slight headache but no other sequelae were observed.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiemetics and antinauseants
ATC Code: A04A

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

Granisetron is effective as an oral prophylactic in abolishing the retching and vomiting evoked by cytostatic therapy.

5.2 Pharmacokinetic properties

Absorption:

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

Distribution:

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

Biotransformation:

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 9 hours, with a wide inter-subject variability.

The pharmacokinetics of granisetron demonstrate no marked deviations from linear pharmacokinetics at oral doses up to 2.5-fold of the recommended clinical dose.

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 considered to be 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

Lactose Monohydrate
Cellulose Microcrystalline
Hypromellose
Sodium Starch Glycolate (type A)
Magnesium Stearate
Titanium Dioxide (E171)
Macrogol 400
Polysorbate 80

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

This product does not require any special storage conditions.

6.5. Nature and contents of container

PVC/PVDC aluminium foil opaque blisters in a cardboard carton containing 1,2,4,5,6,7,10,14,20,28,30,50,90,100,150,200,250 and 500 tablets. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

PL 15773/0515

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

06/06/2006

10 DATE OF REVISION OF THE TEXT

06/06/2006

**GRANISETRON 1 MG & 2MG TABLETS
(GRANISETRON HYDROCHLORIDE)
PL 15773/0514-5**

PRODUCT INFORMATION LEAFLET
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 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:

1. What is in *Granisetron Tablets*?
2. What is your medicine used for?
3. Before you take *Granisetron Tablets*
4. How to take *Granisetron Tablets*
5. Possible side effects
6. Storing your *Granisetron Tablets*

**Granisetron 1 mg Tablets
Granisetron 2 mg Tablets**

ratiopharm

1. What is in *Granisetron Tablets*?

Each white tablet contains either 1 mg or 2 mg of the active ingredient granisetron (as the hydrochloride).

They also contain the following inactive ingredients: lactose monohydrate, cellulose microcrystalline, magnesium stearate, titanium dioxide (E171), sodium starch glycolate, Macrogol, hypromellose and polysorbate. The 1 mg strength tablets are marked 'GS' on one side and the 2 mg strength are marked 'GS2' on one side.

Granisetron 1 mg Tablets are available in blister packs of 10 tablets.

Granisetron 2 mg Tablets are available in blister packs of 5 tablets.

Marketing Authorisation Holder:

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

Manufacturer:

Jenson Pharmaceutical Services Limited, Carradine House, 237 Regents Park Road, London, N3 3LF

2. What is your medicine used for?

Granisetron belongs to a group of medicines known as anti-emetics or anti-sickness medicine. The tablets are used to prevent nausea (feeling sick) and vomiting (being sick) following cancer chemotherapy or radiation treatment.

3. Before you take *Granisetron Tablets*

If the answer to any of the following questions is yes, tell your doctor or nurse BEFORE you take your tablets. You may need to be given another medicine instead.

- Are you allergic to Granisetron or any related drugs (other 5-HT₃ receptor antagonists, such as ondansetron) or any of the other ingredients?
- Has this medicine been prescribed for a child under 12 years of age?
- 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?
- Do you have severe constipation?

Pregnancy and breast-feeding

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

Important information about some of the ingredients of *Granisetron Tablets*

This medicine contains lactose. If you have been told by your doctor you have an intolerance to some sugars, contact your doctor before taking this medicine.

4. How to take *Granisetron Tablets*

Granisetron 1 mg Tablets and *Granisetron 2 mg Tablets* should be taken within one hour of starting cancer treatment.

The tablets should be swallowed with a glass of water.

Adults (including the elderly) - Either 1 mg of Granisetron twice a day or 2 mg once a day. The maximum dose is 9 mg over 24 hours. Your doctor may also give you another medicine called Dexamethasone to take as well.

Children - Granisetron Tablets are not suitable for children under 12 years.

Do not take more than your doctor has recommended.

What if you have taken too much?

You should only take the dose that your doctor or nurse has told you. If you take too many tablets, tell your doctor or go to the nearest hospital casualty department **straight away**. Take the container and any remaining tablets with you.

What should you do if you forget to take a tablet?

It is important to take your *Granisetron Tablets* as directed to prevent you feeling sick. If you forget to take a dose, and feel sick, take it as soon as you remember unless it is nearly time for your next dose. **Do not take two doses together to make up for the one you have missed.**

5. Possible side effects

- Like any medicine, Granisetron can cause unwanted effects, 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 some times causes changes in liver function tests.
- If you think your tablets may be causing any other problems, or you are at all worried, talk to your doctor or nurse.

6. Storing your *Granisetron Tablets*

- Your tablets will have an expiry date on the pack. You should not use your tablets after this date.
- There are no special storage precautions for this medicine.
- Remember these tablets have been prescribed just for you. Never offer your tablets to other people. They may not be suitable for them, even if their symptoms seem the same as yours.

Keep *Granisetron Tablets* out of the reach and sight of children

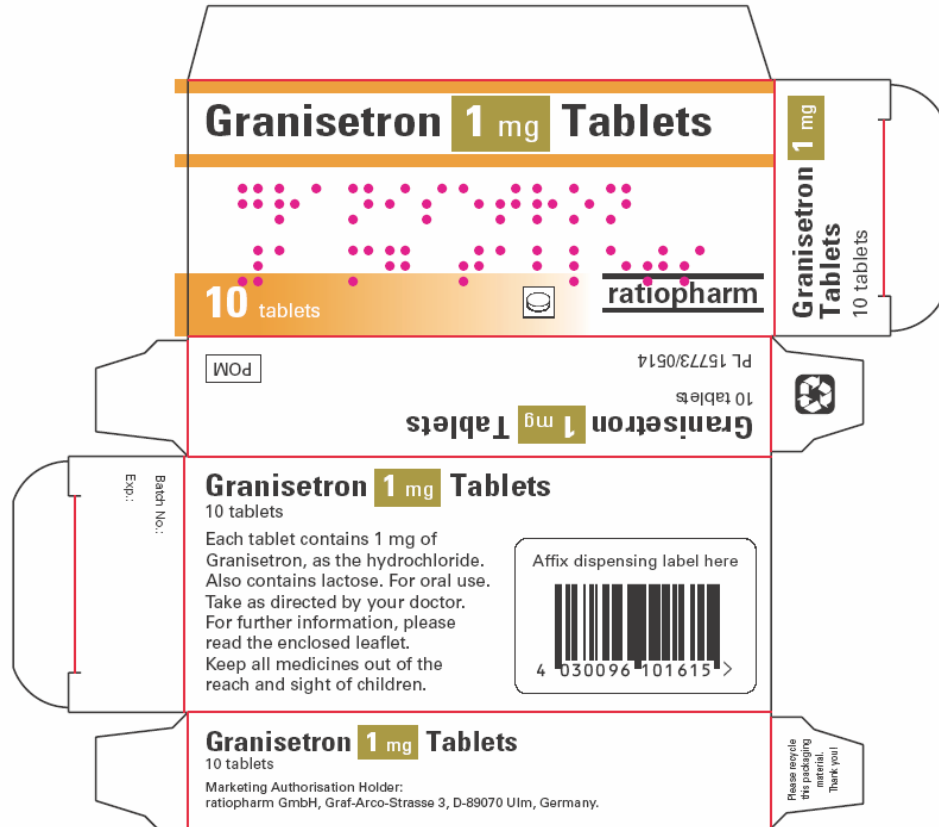
Leaflet dated: February 2006

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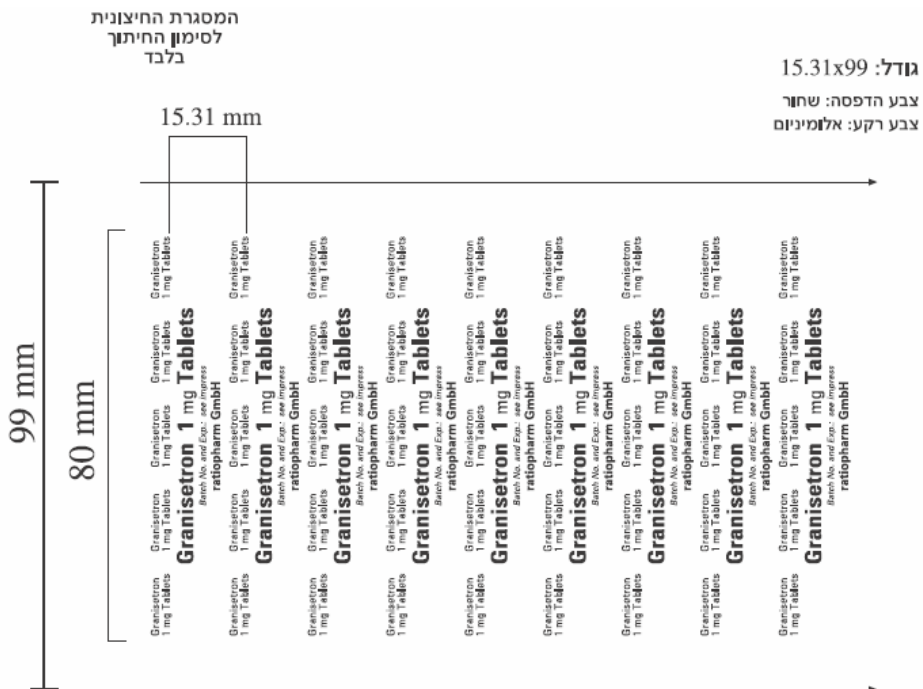
**GRANISETRON 1 MG TABLETS
(GRANISETRON HYDROCHLORIDE)
PL 15773/0514**

LABELLING

CARTON



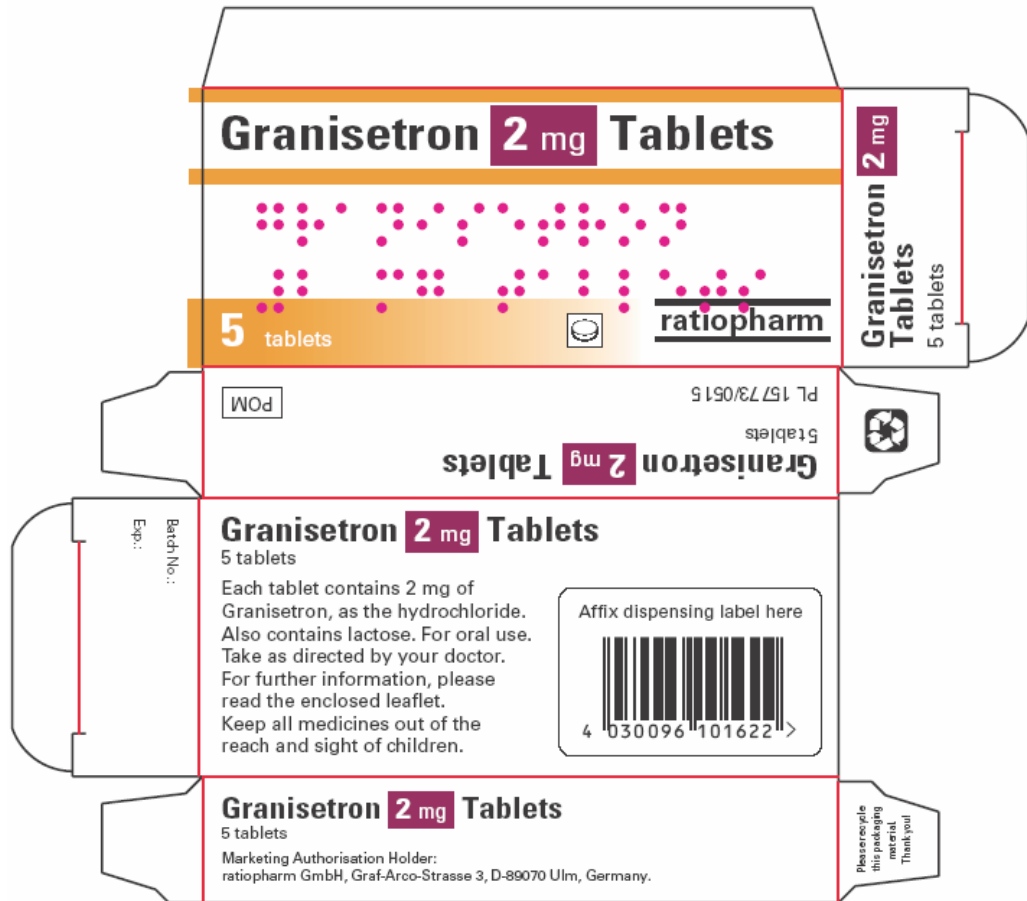
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**GRANISETRON 2 MG TABLETS
(GRANISETRON HYDROCHLORIDE)
PL 15773/0515**

LABELLING

CARTON



FOIL

