

Module 1**1.3 Product Information**

**Applicant: Martindale
Pharmaceuticals Ltd**

**Product: Granisetron Martindale Pharma[®] 1mg/1ml Concentrate
for Solution for Injection/Infusion**

Leaflet

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PACKAGE LEAFLET INFORMATION FOR THE PATIENT

**Granisetron Martindale Pharma
1mg/1ml Concentrate for Solution for Injection/Infusion**

Granisetron 1 mg/1ml
(Concentrate for Solution for Injection/Infusion)

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, please ask your doctor, nurse or pharmacist.
- This medicine has been prescribed for you only. Do not pass it onto others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, nurse or pharmacist. This includes possible side effects not listed in this leaflet.

What is in this leaflet

1. What Granisetron Martindale Pharma is and what it is used for
2. What you need to know before you are given Granisetron Martindale Pharma
3. How you will be given Granisetron Martindale Pharma
4. Possible side effects
5. How to store Granisetron Martindale Pharma
6. Contents of the pack and other information

1. What Granisetron Martindale Pharma is and what it is used for

Granisetron Martindale Pharma contains a medicine called granisetron. This belongs to a group of medicines called '5-HT₃ receptor antagonists' or 'anti-emetics'.

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

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

Granisetron Martindale Pharma will be given to you by a doctor or nurse in a hospital environment.

2. What you need to know before you are given Granisetron Martindale Pharma

Do not take Granisetron Martindale Pharma

- If you are allergic to granisetron or any other ingredients of this medicine (listed in section 6).
- If you are not sure, talk to your doctor, nurse or pharmacist before having the injection.

Warnings and precautions

Talk to your doctor, nurse before taking Granisetron Martindale Pharma if you:

**Applicant: Martindale
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**Product: Granisetron Martindale Pharma® 1mg/1ml Concentrate
for Solution for Injection/Infusion**

- are having problems with your bowel movements because of a blockage of your gut (intestines)
- have heart problems, are being treated for cancer with a medicine that is known to damage your heart or have problems with level of salts, such as potassium, sodium or calcium, in your body (electrolyte abnormalities)
- are taking other '5-HT₃ receptor antagonist' medicines. These include dolasetron, ondansetron used like Granisetron Martindale Pharma in the treatment and prevention of nausea and vomiting.

Other medicines and Granisetron Martindale Pharma

Tell your doctor or nurse if you are taking, have recently taken or might take any other medicines. This is because Granisetron Martindale Pharma can affect the way some medicines work. Also some other medicines can affect the way this injection works. In particular, tell your doctor or nurse if you are taking any of the following medicines:

- medicines used to treat an irregular heartbeat other '5-HT₃ receptor antagonist' medicines such as dolasetron or ondansetron (see "Warnings and precautions with Granisetron Martindale Pharma" above)
- phenobarbital, a medicine used to treat epilepsy
- a medicine called ketoconazole used in the treatment of fungal infections
- the antibiotic erythromycin used to treat bacterial infections.

Pregnancy, breast-feeding and fertility

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

Driving and using machines

Granisetron Martindale Pharma is not likely to affect your ability to drive or use any tools or machines.

3. How you will be Granisetron Martindale Pharma

The injection will be given to you by your doctor or nurse. The dose of Granisetron Martindale Pharma varies from one patient to another. It depends on your age, weight and whether you are being given the medicine to prevent, or treat nausea and vomiting. The doctor will work out how much to give you. Granisetron Martindale Pharma can be given as an injection into the veins (intravenous).

Prevention of feeling or being sick following radio- or chemotherapy

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

Treatment of feeling or being sick following radio- or chemotherapy

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

Combination with steroids

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Pharmaceuticals Ltd****Product: Granisetron Martindale Pharma® 1mg/1ml Concentrate
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The effect of the injection may be improved by the use of medicines called adrenocortical steroids. The steroid will be given either as a dose between 8 and 20 mg dexamethasone before your radio- or chemotherapy or as 250 mg methylprednisolone, which will be given both before and after your radio- or chemotherapy.

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

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

Treatment of feeling or being sick following surgery

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

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

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

If you are given too much Granisetron Martindale Pharma or a dose is missed.

As this injection will be given to you 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 concerned about your treatment, please talk to your doctor or nurse. Symptoms of overdose include mild headaches. You will be treated depending on your symptoms.

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

4. Possible side effects

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

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

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

Very common: affects more than 1 user in 10

Common: affects 1 to 10 users in 100

Uncommon: affects up to 1 to 10 users in 1,000

Very common	<ul style="list-style-type: none">• headache• constipation. Your doctor will monitor your condition.
Common	<ul style="list-style-type: none">• problems sleeping (insomnia)• changes in how your liver is working

**Applicant: Martindale
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	shown by blood tests
	<ul style="list-style-type: none">• diarrhoea.
Uncommon	<ul style="list-style-type: none">• skin rashes or an allergic skin reaction or “nettle rash” or “hives” (urticaria). The signs may include red, raised itchy bumps• changes in heartbeat (rhythm) and changes seen on ECG readings (electrical recordings of the heart)• abnormal involuntary movements, such as shaking, muscle rigidity and muscle contractions.

If you get any side effects, talk to your doctor, nurse or pharmacist. This includes possible side effects not listed in this leaflet.

5. How to store Granisetron Martindale Pharma

Keep this medicine out of the sight and reach of children.

Granisetron Martindale Pharma should be kept in the original carton, in order to protect from light and should not be stored above 30°C. The ampoules should not be frozen

The expiry date is stated on end-flap of the outer carton, as well as on the ampoule label, please make sure this has not expired. The doctor or nurse will also check that the product does not show signs of visible damage or discoloration.

Do not throw away this medicine via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer required. These measures will help to protect the environment.

This product should only be used in a hospital environment.

6. Contents of the pack and other information

What Granistron Martindale Pharma contains

Granisetron Martindale Pharma contains the active substance Granisetron 1 mg/ml (as the hydrochloride). The other ingredients are Sodium Chloride, Citric Acid Monohydrate, Hydrochloric Acid, Sodium Hydroxide for pH (acidity) adjustment and Water for Injection.

This medicinal product contains less than 1 mmol sodium (23 mg) per 1ml, i.e. essentially ‘sodium-free’.

What Granistron Martindale Pharma looks like and contents of the pack

The injection is supplied in 1 ml glass ampoules. Each ampoule contains a clear, colourless solution, free from visible particles. The 1 ml ampoule contains 1 mg of granisetron (as hydrochloride).

Marketing Authorisation Holder:

Martindale Pharmaceuticals Ltd

Module 1**1.3 Product Information**

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Bampton Road, Harold Hill, Romford, Essex RM3 8UG United Kingdom

Manufacturer:

Macarthys Laboratories trading as Martindale Pharmaceuticals
Bampton Road, Harold Hill, Romford, Essex RM3 8UG United Kingdom

This leaflet was last revised in September 2011

Product licence numbers: PL 00156/0345
PA 0361/029/001

TECHNICAL PRESCRIBING INFORMATION

**Granisetron Martindale Pharma
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Granisetron 1 mg/1ml
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Product:

Granisetron Martindale Pharma 1mg/1ml Concentrate for Injection/Infusion

Composition

The active ingredient is granisetron. Each ml solution for injection contains 1 mg of Granisetron (as hydrochloride). Also contains Sodium Chloride, Citric Acid Monohydrate, Hydrochloric Acid, Sodium Hydroxide and Water for Injections.

Applicant: Martindale Pharmaceuticals Ltd	Product: Granisetron Martindale Pharma® 1mg/1ml Concentrate for Solution for Injection/Infusion
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Therapeutic indications

Granisetron Martindale Pharma is indicated in adults for the prevention and treatment of

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

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

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

Posology and method of administration**Posology**

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

Prevention (acute and delayed nausea)

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

Treatment (acute nausea)

A dose of 1-3 mg (10-40 µg/kg) of Granisetron Martindale Pharma solution for injection should be administered. Further maintenance doses of Granisetron Martindale Pharma solution for injection may be administered at least 10 minutes apart. The maximum dose to be administered over 24 hours should not exceed 9mg.

Combination with adrenocortical steroid

The efficacy of parenteral granisetron may be enhanced by an additional intravenous dose of an adrenocortical steroid e.g. by 8-20 mg dexamethasone administered before the start of the cytostatic therapy or by 250 mg methyl-prednisolone administered prior to the start and shortly after the end of the chemotherapy.

Paediatric population

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

Post-operative nausea and vomiting (PONV)

Applicant: Martindale Pharmaceuticals Ltd	Product: Granisetron Martindale Pharma® 1mg/1ml Concentrate for Solution for Injection/Infusion
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A dose of 1 mg (10 µg/kg) of Granisetron Martindale Pharma solution for injection should be administered by slow intravenous injection. The maximum dose of Granisetron Martindale Pharma to be administered over 24 hours should not exceed 3 mg. For the prevention of PONV, administration should be completed prior to induction of anaesthesia.

Special populations

Elderly and renal impairment

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

Hepatic Impairment

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

Method of administration

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

Contraindications

Hypersensitivity to the active substance or any of the excipients.

Special warnings and precautions for use

Granisetron Martindale Pharma may reduce lower bowel motility; patients with signs of sub-acute intestinal obstruction should be monitored following its administration.

As for other 5-HT₃ antagonists, ECG changes including QT interval prolongation have been reported with granisetron. In patients with pre-existing arrhythmias or cardiac conduction disorders this might lead to clinical consequences. Therefore caution should be exercised in patients with cardiac co-morbidities, on cardiotoxic chemotherapy and/or with concomitant electrolyte abnormalities. Cross-sensitivity between 5-HT₃ antagonists (e.g. dolasetron, ondansetron) has been reported.

Interaction with other medicinal products and other forms of interaction

As for other 5-HT₃ antagonists, cases of ECG modifications including QT prolongation have been reported with granisetron. In patients concurrently treated with medicinal products known to prolong QT interval and/or which are arrhythmogenic, this may lead to clinical consequences.

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

**Applicant: Martindale
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No specific interaction studies have been conducted in anaesthetised patients.

Fertility, pregnancy and lactation

Pregnancy

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

Breast-feeding

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

Fertility

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

Driving and using machines

Granisetron Martindale Pharma is not expected to impair the ability to drive or use machines.

Undesirable Effects

Summary of the safety profile

The most frequently reported adverse reactions for granisetron are headache and constipation which may be transient. ECG changes including QT prolongation have been reported with granisetron.

Tabulated summary of adverse reactions

The following table of listed adverse reactions is derived from clinical trials and post-marketing data associated with granisetron and other 5-HT₃ antagonists.

Frequency categories are as follows:

Very common: $\geq 1/10$;

Common $\geq 1/100$ to $< 1/10$;

Uncommon $\geq 1/1,000$ to $< 1/100$

Rare ($\geq 1/10,000$ to $< 1/1,000$)

Very rare ($< 1/10,000$)

<i>Immune system disorders</i>	
Uncommon	Hypersensitivity reactions e.g. anaphylaxis, urticaria
<i>Psychiatric disorders</i>	
Common	Insomnia
<i>Nervous system disorders</i>	
Very common	Headache
Uncommon	Extrapyramidal Reactions
<i>Cardiac disorders</i>	

Module 1**1.3 Product Information****Applicant: Martindale
Pharmaceuticals Ltd****Product: Granisetron Martindale Pharma® 1mg/1ml Concentrate
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Uncommon	QT prolongation
<i>Gastrointestinal disorders</i>	
Very common	Constipation
Common	Diarrhoea
<i>Hepatobiliary disorders</i>	
Common	Elevated hepatic transaminases*
<i>Skin and subcutaneous tissue disorders</i>	
Uncommon	Rash

*Occurred at a similar frequency in patients receiving comparator therapy

Description of selected adverse reactions

As for other 5-HT₃ antagonists, ECG changes including QT prolongation have been reported with granisetron.

Overdose

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

Pharmacodynamics

Pharmacotherapeutic group: Antiemetics and antinauseants, Serotonin (5-HT₃) antagonists.

ATC code: A04AA02

Neurological mechanisms, serotonin-mediated nausea and vomiting

Serotonin is the main neurotransmitter responsible for emesis after chemo- or radio-therapy. The 5-HT₃ receptors are located in three sites: vagal nerve terminals in the gastrointestinal tract and chemoreceptor trigger zones located in the *area postrema* and the *nucleus tractus solitarius* of the vomiting center in the brainstem. The chemoreceptor trigger zones are located at the caudal end of the fourth ventricle (*area postrema*). This structure lacks an effective blood-brain barrier, and will detect emetic agents in both the systemic circulation and the cerebrospinal fluid. The vomiting centre is located in the brainstem medullary structures. It receives major inputs from the chemoreceptor trigger zones, and a vagal and sympathetic input from the gut.

Following exposure to radiation or catotoxic substances, serotonin (5-HT) is released from enterochromaffine cells in the small intestinal mucosa, which are adjacent to the vagal afferent neurons on which 5-HT₃ receptors are located. The released serotonin activates vagal neurons via the 5-HT₃ receptors which lead ultimately to a severe emetic response mediated via the chemoreceptor trigger zone within the *area postrema*.

Mechanism of action

Granisetron is a potent anti-emetic and highly selective antagonist of 5-hydroxytryptamine (5-HT₃) receptors. Radioligand binding studies have

Applicant: Martindale Pharmaceuticals Ltd	Product: Granisetron Martindale Pharma® 1mg/1ml Concentrate for Solution for Injection/Infusion
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demonstrated that granisetron has negligible affinity for other receptor types including 5-HT and dopamine D₂ binding sites.

Chemotherapy- and radiotherapy-induced nausea and vomiting

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

Post-operative nausea and vomiting

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

Pharmacological properties of granisetron

Interaction with neurotropic and other active substances through its activity on P 450-cytochrome has been reported.

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

Although QT-prolongation has been observed with 5-HT₃ receptors antagonist, this effect is of such occurrence and magnitude that it does not bear clinical significance in normal subjects. Nonetheless it is advisable to monitor both ECG and clinical abnormalities when treating patients concurrently with drugs known to prolong the QT.

Paediatric use

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

Pharmacokinetics

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

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

Distribution

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

Biotransformation

Granisetron is metabolized primarily in the liver by oxidation followed by conjugation. The major compounds are 7-OH-granisetron and its sulphate and glucuronide conjugates. Although antiemetic properties have been observed for 7-OH-granisetron

Applicant: Martindale Pharmaceuticals Ltd	Product: Granisetron Martindale Pharma® 1mg/1ml Concentrate for Solution for Injection/Infusion
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and indazoline N-desmethyl granisetron, it is unlikely that these contribute significantly to the pharmacological activity of granisetron in man. In vitro liver microsomal studies show that granisetron's major route of metabolism is inhibited by ketoconazole, suggestive of metabolism mediated by the cytochrome P-450 3A subfamily.

Elimination

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

Pharmacokinetics in special populations**Renal failure**

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

Hepatic impairment

In patients with hepatic impairment due to 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.

Elderly patients

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

Paediatrics

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

Incompatibilities

The medicinal product must not be mixed with other medicinal products except those mentioned below.

Shelf life

Unopened: 2 years

Once opened, use immediately. For single use only. Discard any remaining portion.

Special precautions for storage

Do not store above 30°C. Keep the ampoules in the outer carton in order to protect from light. Do not freeze.

Special precautions for disposal

Dilute before use. For single use only. Discard any unused contents appropriately.

Preparing the infusion

Applicant: Martindale Pharmaceuticals Ltd	Product: Granisetron Martindale Pharma® 1mg/1ml Concentrate for Solution for Injection/Infusion
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Children: To prepare the dose of 40 µg/kg, the appropriate volume is withdrawn and diluted with infusion fluid to a total volume of 10 to 30 ml. Any one of the following solutions may be used: 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; or 10% Mannitol Injection. No other diluents should be used.

Preparing the slow intravenous injection

Adults: A single dose of 1 mg of Granisetron Martindale Pharma should be diluted to 5 ml and administered as a slow intravenous injection (over 30 seconds).

Ideally, intravenous infusions of Granisetron Martindale Pharma should be prepared at the time of administration. After dilution (see above), or when the container is opened for the first time, 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 Martindale Pharma infusions must be prepared under appropriate aseptic conditions. The product does not contain a preservative. Any unused portion should be discarded

MA Holder

Martindale Pharmaceuticals Ltd, Bampton Road, Harold Hill, Romford, Essex, RM3 8UG, UK.

MA Numbers

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