New Zealand Datasheet

1 PRODUCT NAME
GRANIREX

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Granisetron hydrochloride injection

3 PHARMACEUTICAL FORM
GRANIREX is administered as the hydrochloride salt, granisetron hydrochloride.

GRANIREX 0.1 mg/ml injection solution single-use vials contain a clear colourless solution equivalent to 0.1 mg of granisetron per 1 mL. The vial has a fill volume of 1 mL.

GRANIREX 1 mg/ml injection solution vials contain a clear colourless solution equivalent to 1 mg of granisetron per 1 mL. The single-use vials have a 1 mL fill volume and the multi-use vials have a 4 mL fill volume.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Adults:
Granisetron injection is indicated for use in adults for:
1. The prevention and treatment of nausea and vomiting induced by cytotoxic chemotherapy;
2. The prevention of nausea and vomiting induced by radiotherapy.
3. The prevention and treatment of post-operative nausea and vomiting.

Paediatric:
Granisetron injection is indicated for the prevention of nausea and vomiting induced by cytotoxic chemotherapy.

4.2 Dose and method of administration
Standard Dosage by indication for adult and paediatric patients are shown below.
Indication: Chemotherapy Induced Nausea and Vomiting (CINV)
Adults
Prevention of nausea and vomiting in adults
A single dose of 3 mg of Granisetron injection should be administered as an intravenous infusion, diluted in 20 to 50 mL infusion fluid and administered over 5 minutes prior to the start of chemotherapy. The infusion should be commenced within 30 minutes before the start of chemotherapy.

Prophylactic administration of Granisetron injection should be completed prior to the start of chemotherapy.

In clinical trials, the majority of patients have required only a single dose of granisetron to control nausea and vomiting over 24 hours.

Treatment of established nausea and vomiting in adults
A single dose of 1 mg of Granisetron injection should be administered as a 5 minute infusion. Further treatment doses of Granisetron injection may be administered if required at least 10 minutes apart. The maximum dose of Granisetron injection is 9 mg/24 hours.

In trials, patients have received a total dose of 160 µg/kg of intravenous granisetron in one day.

There is also clinical experience in patients receiving a total of 600 µg/kg of intravenous granisetron over 5 days.

Paediatric
Prevention of nausea and vomiting in paediatric patients- The recommended intravenous dose of Granisetron injection in paediatric patients is 20 µg to 40 µg/kg body weight (up to 3 mg), which should be administered as an intravenous infusion, diluted in 10 to 30 mL infusion fluid and administered over 5 minutes, no more than 30 minutes before the start of chemotherapy.

Indication: Radiotherapy Induced Nausea and Vomiting
Adults
Prevention of nausea and vomiting in adults
A single dose of 3 mg of Granisetron injection should be administered as an intravenous infusion, diluted in 20 to 50 mL infusion fluid and administered over 5 minutes prior to the start of radiotherapy.

Treatment of nausea and vomiting in adults
There is insufficient information to recommend the intravenous administration of Granisetron injection in the treatment of RINV in adult patients.

Paediatric
There is insufficient information to recommend the intravenous administration of Granisetron injection in the prevention or treatment of RINV in paediatric patients.

Indication: Post-operative Nausea and Vomiting
Adults
Prevention of post-operative nausea and vomiting in adults
A single dose of 1 mg of Granisetron injection should be administered as a 30 second intravenous injection prior to induction of anaesthesia.

Treatment of established post-operative nausea and vomiting in adults
A single dose of 1 mg of Granisetron injection should be administered by intravenous injection over 30 seconds.

Patients undergoing anaesthesia for elective surgery have received a total dose of 3 mg granisetron intravenous in one day.

Paediatric
There is insufficient information to recommend the intravenous use of Granisetron injection in the prevention or treatment of post-operative nausea and vomiting in paediatric patients.

Special Dosage Instructions
No dosage adjustment is required for the elderly, renally impaired or hepatically impaired (see Pharmacokinetics in Special Populations).

Combination with a Corticosteroid
The efficacy of IV Granisetron injection can be enhanced by the addition of an intravenous corticosteroid. For example, 8-20 mg of dexamethasone administered prior to the start of cytostatic therapy, or 250 mg methlyprednisolone prior to the start of chemotherapy and again just after the end of chemotherapy.

Preparing the Infusion
Adults: To prepare the dose of 3 mg, withdraw 3 mL from the ampoule and dilute with a compatible infusion fluid to a total volume of 20 to 50 mL, in either 0.9% sodium chloride or 5% glucose.

Paediatric patients: To prepare the dose of 40 µg/kg, the appropriate volume is withdrawn (up to 3 mL from the ampoule) and diluted with infusion fluid (as for adults) to a total volume of 10 to 30 mL.

The injectable presentations contain no antimicrobial agent. Use once and discard any residue.

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

As a general precaution, Granisetron injection should not be mixed in solution with other drugs other than dexamethasone sodium phosphate.

Admixtures of granisetron hydrochloride and dexamethasone sodium phosphate are compatible at concentrations of 10 to 60 µg/mL granisetron and 80 to 480 µg/mL dexamethasone phosphate in either 0.9% sodium chloride or 5% glucose intravenous infusion fluids. The admixture will have a shelf-life of 24 hours.

Parenteral drug products should be inspected visually for particulate matter and discolouration before administration whenever solution and container permit.

4.3 Contraindications

GRANIREX is contraindicated in patients hypersensitive to granisetron and excipients.

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 closely following administration of GRANIREX.

As with other 5-HT3 antagonists, cases of ECG modifications including QT prolongation have been reported with granisetron. The ECG changes with granisetron were minor, generally not of clinical significance and specifically, there was no evidence of proarrhythmia. However, 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 cardio-toxic chemotherapy and/or with concomitant electrolyte abnormalities.

In healthy subjects, no clinically relevant effects on resting EEG or on the performance of psychometric tests were observed after IV granisetron at any dose tested (up to 200 µg/kg).

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

The 1 mg /ml strength injection solution contains the preservatives methyl paraben and propyl paraben, which may be unsuitable for some patients.

4.5 Interaction with other medicines and other forms of interaction

Granisetron does not induce or inhibit the cytochrome P450 drug metabolising enzyme system in rodent studies. In humans, hepatic enzyme induction with phenobarbital resulted in an increase in total plasma clearance of intravenous granisetron of approximately one-quarter.

In healthy human subjects, granisetron has been safely administered in humans with benzodiazepines, neuroleptics and anti-ulcer medications, commonly prescribed with

antiemetic treatments. Additionally, granisetron has shown no apparent drug interaction with emetogenic cancer chemotherapies.

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, the activity of the cytochrome P450 subfamily 3A4 (involved in the metabolism of some of the main narcotic analgesic agents) is not modified by granisetron.

As for other 5-HT3 antagonists, cases of ECG modifications including QT prolongation have been reported with granisetron. The ECG changes with granisetron were minor, generally not of clinical significance and specifically, there was no evidence of proarrhythmia. However, in patients concurrently treated with drugs known to prolong QT interval and/or are arrhythmogenic, this may lead to clinical consequences.

4.6 Fertility, pregnancy and lactation

Use in Pregnancy

There is no experience of granisetron in human pregnancy. Animal studies have shown no teratogenic effects in rats or rabbits at intravenous doses up to 9 and 3 mg/kg/day respectively.

Time weighted systemic exposure (maternal plasma AUC) at the highest intravenous dose in rats was about 7 times higher than that in humans at therapeutic dose levels, but insufficient data are available for a similar comparison in rabbits. Because of the low safety margin indicated by the animal studies and because animal reproduction studies are not always predictive of human response, Granisetron injection should be used during pregnancy only if clearly needed.

Breast feeding

A study in lactating rats showed that the rate of excretion in milk after IV dosing is less than 1% of the dose per hour, and that at least some of this is absorbed by the offspring.

There are no data on the excretion of granisetron in human breast milk, therefore use of the drug during lactation should be limited to situations where the potential benefit to the mother justifies the potential risk to the nursing infant.

Fertility

In the rat, granisetron had no untoward effect on reproductive performance, fertility or on pre- and post-natal development. Teratogenic effects were not observed in rats or rabbits.

4.7 Effects on ability to drive and use machines

There are no data on the effect of granisetron on the ability to drive, however there have been occasional reports of somnolence in clinical studies which should be taken into account.

4.8 Undesirable effects

Granisetron has been well tolerated in human studies. The most frequently reported adverse reactions for granisetron are headache and constipation which may be transient. ECD changes including QT prolongation have been reported with granisetron (*see* section 4.4).

Table 1 gives the comparative frequencies of the five commonly reported adverse events (>3%) in patients receiving granisetron injection, 40 µg/kg, in single-day chemotherapy trials. These patients received chemotherapy, primarily cisplatin, and intravenous fluids during the 24-hour period following granisetron injection administration.

Table 1. Principal Adverse Events in Clinical Trials Single-Day Chemotherapy

	Percent of Patients with an Event	
Adverse Event	**Granisetron Injection[1] 40 µg/kg (n=1,268)**	**Comparator[2] (n=422)**
Headache Asthenia Somnolence	14% 5% 4%	6% 6% 15%
Diarrhoea Constipation	4% 3%	6% 3%

1 Adverse events were generally recorded over 7 days post-granisetron injection administration.
2 Metoclopramide/dexamethasone and phenothiazines/dexamethasone.

In the absence of a placebo group, there is uncertainty as to how many of these events should be attributed to granisetron, except for headache, which was clearly more frequent than in comparison groups.

Adverse events reported in clinical trials other than those in the tables above are listed below. All adverse experiences are included in the list except those reported in terms so general as to be uninformative and those experiences for which the drug cause was remote. It should however be noted that causality has not necessarily been established.

Events are listed within body systems and categorised by frequency according to the following definitions: very common events reported at a frequency of greater or equal to 1/10 patients; common events reported at a frequency of greater or equal to 1/100 patients; uncommon events reported at a frequency of less than 1/100 but greater or equal to 1/1,000 patients; rare events reported at a frequency of less than 1/1,000 patients.

Body as a whole: *Common:* fever.

Cardiovascular: *Common:* hypertension; *Rare*: hypotension, arrhythmias, sinus bradycardia, atrial fibrillation, varying degrees of A-V block, ventricular ectopy including non-sustained tachycardia, ECG abnormalities, angina pectoris, syncope.

Hypersensitivity: *Rare:* hypersensitivity reactions (e.g. anaphylaxis, shortness of breath, hypotension, urticaria).

Hepatic: *Common:* transient increases in AST and ALT. These are generally within the normal range and have been reported at similar frequency in patients receiving comparator therapy.

Nervous system: *Common:* agitation, anxiety, CNS stimulation, dizziness, insomnia, somnolence; *Rare*: extrapyramidal syndrome (only in presence of other drugs associated with this syndrome).

Dermatological: *Common:* skin rashes.

Special Senses: *Common:* taste disorder.

Other common events often associated with chemotherapy also have been reported: leukopaenia, decreased appetite, anaemia, alopecia, thrombocytopaenia.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

4.9 Overdose

In the case of overdosage with GRANIREX, symptomatic treatment should be given. Overdose with the intravenous of granisetron has occurred. Overdosage of up to 38.5 mg of granisetron hydrochloride as a single injection has been reported without symptoms or only the occurrence of a slight headache. There is no specific antidote for Granisetron.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiemetics and antinauseants, Serotonin (5-HT3) antagonists - ATC code: A04AA02

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 HT, alpha$_1$ and alpha$_2$, beta-adrenoreceptors, histamine H_1, picrotoxin, benzodiazepine, opioid and dopamine D2 binding sites.

Antagonism of 5-HT_3 receptors located peripherally on vagal nerve terminals and centrally in the chemoreceptor trigger zone in the area postrema, is one of the most effective pharmacological methods of preventing cytotoxic-induced emesis. Mucosal enterochromaffin cells release serotonin during chemotherapy-induced emesis. Serotonin stimulates 5-HT_3 receptors and evokes a vagal afferent discharge to subsequently induce emesis. Animal pharmacological studies have shown that in binding to 5-HT_3 receptors, granisetron blocks serotonin stimulation, and is effective in alleviating the retching and vomiting evoked by cytostatic treatment. In the ferret animal model, a single granisetron injection prevented vomiting due to high-dose cisplatin or arrested vomiting within 5 to 30 seconds.

In healthy subjects, granisetron produced no consistent or clinically important changes in pulse rate, blood pressure or ECG. Granisetron did not affect the plasma levels of prolactin or aldosterone.

Granisetron injection showed no effect on gut transit time in normal volunteers given single doses up to 200 µg/kg. However, single and multiple doses of granisetron orally, slowed colonic transit time in normal volunteers.

CLINICAL TRIALS

Intravenous Administration

Single-Day Chemotherapy

Cisplatin-Based Chemotherapy: In a double-blind, placebo-controlled study in 28 patients, Granisetron Injection administered as a single intravenous infusion of 40 µg/kg, was significantly more effective than placebo in preventing nausea and vomiting induced by cisplatin chemotherapy.

Granisetron Injection was also evaluated in a randomised dose response study of cancer patients receiving cisplatin >75 mg/m^2. Additional chemotherapeutic agents included: anthracyclines, carboplatin, cytostatic antibiotics, folic acid derivatives, methylhydralazine,

nitrogen mustard analogs, podophyllotoxin derivatives, pyrimidine analogs and vinca alkaloids. Granisetron Injection doses of 10 and 40 µg/kg were superior to 2 µg/kg in preventing cisplatin-induced nausea and vomiting.

Moderately Emetogenic Chemotherapy: Granisetron Injection, 40 µg/kg, was compared with the combination of chlorpromazine (50 to 200 mg/24 hours) and dexamethasone (12 mg) in patients treated with moderately emetogenic chemotherapy, including primarily carboplatin >300 mg/m^2, cisplatin 20 to 50 mg/m^2 and cyclophosphamide >600 mg/m^2. Granisetron Injection was superior to the chlorpromazine/dexamethasone regimen in preventing nausea and vomiting.

Repeat Cycle Chemotherapy
In an uncontrolled trial, 75 cancer patients received granisetron Injection, 40 µg/kg prophylactically, for three cycles of chemotherapy. 31 patients received it for at least four cycles and 8 patients received it for at least six cycles. Granisetron Injection efficacy remained relatively constant over the first six repeat cycles, with complete response rates (no vomiting and no moderate or severe nausea in 24 hours) of 65-70%. No patients were studied for more than 9 cycles.

During the clinical trial programme, there were 26 reports of cardiac arrest. Of these, 25 were considered to be unrelated to granisetron administration and were attributed to the underlying disease or concomitant cytostatic medication with time of onset up to 4 months after initiation of therapy.

In the one case where granisetron administration was causally related, the patient experienced cardiac arrest as part of a severe allergic reaction. This event was not related to any direct cardiotoxic effect of granisetron. A full recovery was made on discontinuation of therapy.

Of the 40 reports of renal failure, causality was assigned in 37 cases. All 37 were considered to be unrelated to granisetron administration and were attributed to the underlying disease or cisplatin, a known nephrotoxic agent.

Paediatric
Granisetron injection 20 µg/kg was compared to chlorpromazine (0.5 mg/kg) plus dexamethasone (2 mg/m^2) in 88 paediatric patients treated with ifosfamide > 3 g/m^2 for two or three days. Granisetron was administered on each day of ifosfamide treatment. At 24 hours, 22% of granisetron patients achieved complete response (no vomiting and no moderate or severe nausea in 24 hours) compared with 10% on the chlorpromazine/dexamethasone regimen. The median number of vomiting episodes was significantly lower in patients receiving granisetron than in patients receiving the combination of chlorpromazine/ dexamethasone (1.5 vs 7).

The efficacy and safety of intravenous doses of 10, 20 and 40 µg/kg were compared in 80 paediatric patients undergoing highly emetogenic chemotherapy. The median number of vomiting episodes were 2, 3, and 1 and the percentage of patients with no more than one vomiting episode were 48%, 42% and 56% respectively. There were no dose related safety issues.

Granisetron administered intravenously has been shown to be effective in paediatric patients aged 2 years and above for the prevention of nausea and vomiting induced by cytotoxic chemotherapy. There is insufficient information to recommend intravenous administration of granisetron for the treatment of paediatric patients with nausea and vomiting induced by cytotoxic chemotherapy.

Radiotherapy

Granisetron injection 3 mg was compared to a combination of intravenous (i.v.) metoclopramide (20 mg), dexamethasone (6 mg/m^2), and lorazepam (2 mg) in 30 patients to assess the efficacy and safety of granisetron for prophylaxis and control of radiotherapy induced emesis. The study drug was administered 1 hour before starting radiation therapy. The anti-emetic efficacy of granisetron was significantly more effective than the standard regimen of metoclopramide/dexamethasone/lorazepam in preventing radiotherapy induced emesis.

Very limited data are available on the use of granisetron in the treatment of nausea and vomiting induced by radiotherapy.

Post-operative nausea and vomiting
Prevention: Granisetron injection 0.1 mg, 1.0 mg or 3.0 mg, was compared to placebo in a double-blind study to assess the efficacy and safety of granisetron in the prevention of post-operative nausea and vomiting (PONV) in 538 patients. Granisetron was given as a 30 second injection prior to induction of anaesthesia. Patient groups receiving 1.0 mg and 3.0 mg granisetron responded significantly better than those in the 0.1 mg group.

Treatment: Granisetron injection 0.1 mg, 1.0 mg or 3.0 mg, was compared to placebo in a double-blind study to assess the efficacy and safety of granisetron in 519 patients experiencing post-operative vomiting or severe nausea. In the 24 hour period after the day of surgery, patients receiving granisetron were less likely to experience nausea and vomiting than those receiving placebo.

5.2 Pharmacokinetic properties

A linear pharmacokinetic relationship was found after IV administration up to 4-fold the recommended dose.

Distribution
Granisetron is extensively distributed with a mean volume of distribution of approximately 3L/kg; plasma protein binding is approximately 65%, and granisetron distributes freely between plasma and red blood cells.

Biotransformation
Clearance is predominantly via hepatic metabolism and is rapid in most subjects. Granisetron metabolism involves N-demethylation and aromatic ring oxidation followed by conjugation. Animal studies suggest some metabolites of granisetron may also have 5-HT3 receptor antagonist activity. However, in humans the metabolites are present in very low concentrations and are thought not to contribute to the pharmacological action.

Elimination
Mean plasma half-life of granisetron in patients is 9 hours with wide inter-subject variability. The plasma concentration of granisteron is not clearly correlated with antiemetic efficacy. Clinical benefit may be conferred even when granisetron is not detectable in plasma.

Urinary excretion of unchanged granisetron averages 12% of the dose in 48 hours, whilst the remainder is excreted as metabolites; 47% in the urine and 34% in the faeces.

Pharmacokinetics in Special Populations Elderly:
In elderly subjects after single intravenous doses, pharmacokinetic parameters were within the range found for younger healthy volunteers. Renal Impairment: 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 clearance of granisetron was approximately halved compared to patients without hepatic impairment. However, no dosage

adjustment is recommended.

5.3 Preclinical safety data

In a 24 month carcinogenicity study, mice were treated with granisetron in the diet at 1, 5 or 50 mg/kg/day. There was a statistically significant increase in the incidence of hepatocellular carcinomas in males and of hepatocellular adenomas in females dosed with 50 mg/kg/day. The incidence of hepatic tumours was not affected at 1 mg/kg/day.

In a 24 month carcinogenicity study, rats were treated with granisetron in the diet at 1,5 or 50 mg/kg/day (reduced to 25 mg/kg/day at week 59 because of toxicity). Systemic exposure at the highest dose level was 1.7 times higher than that in humans at the recommended dose. There was a statistically significant increase in the incidence of hepatocellular carcinomas and adenomas in males dosed with 5 mg/kg/day and above, and in females dosed with 50 mg/kg/day. No increase in liver tumours was observed in rats at a dose of 1 mg/kg/day in males and 5 mg/kg/day in females.

Experimental evidence in rats shows that granisetron exhibits the characteristics of a promoter of liver tumours with a clear no-effect dose of 1 mg/kg. The probable mechanism for this effect is sustained liver cell hyperplasia. In a study in which rats were treated for 12 months with 100 mg/kg/day, the observed promoting effects were reversible upon cessation of treatment. Additionally, there was no adverse effect on the liver of dogs treated orally for 12 months with granisetron 5 mg/kg/day.

Granisetron did not cause gene mutation in bacterial assays in Salmonella and E.coli or in a mouse lymphoma cell assay. No evidence of chromosomal damage was observed in human lymphocytes in vitro, or in a mouse micronucleus test. There was no evidence of DNA damage in assays of unscheduled DNA synthesis (UDS) in rat hepatocytes in vitro, or ex vivo. There was an apparent increase in UDS in HeLa cells exposed to granisetron in vitro when DNA synthesis was measured by scintillation counting of incorporated radioactive thymidine. However, when this test was repeated using a more definitive autoradiographic method, the test was negative for UDS. It is likely that the apparent UDS in the initial study was, in fact, a reflection of DNA synthesis in cells undergoing normal division (mitogenic activity).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

0.1 mg/ml Injection: citric acid monohydrate, sodium chloride, hydrochloric acid or sodium hydroxide (for pH adjustment), water for injections

1 mg/ml Injection: citric acid monohydrate, sodium chloride, methyl hydroxybenzoate, propyl hydroxybenzoate, hydrochloric acid or sodium hydroxide (for pH adjustment), water for injections

6.2 Incompatibilities

This product must not be mixed with other medicinal products except those mentioned in section 4.2.

6.3 Shelf life

Shelf life is 24 months (2 years) from manufacture.

6.4 Special precautions for storage

GRANIREX injection solution vials should be stored at or below 25°C and protected from direct sunlight. Do not freeze.

GRANIREX injection solution vials has been shown to be stable for at least 24 hours in the cited solutions (see section 4.2) when stored at ambient temperature (15-25°C) in normal indoor illumination (natural daylight supplemented by fluorescent light). In order to reduce microbiological hazards, it is recommended that the infusion be commenced as soon as practicable after its preparation, and should be completed within 24 hours.

As a general precaution, GRANIREX injection solution should not be mixed in solution with other medicines. Parenteral drug products should be inspected visually for particulate matter and discolouration before administration whenever solution and container permit.

Discard any unused portion after opening the vials.

6.5 Nature and contents of container

GRANIREX 0.1 mg/ml injection solution is for single-use and is supplied in clear glass vials packaged in boxes of 1 vial, with a 1 mL fill volume.

GRANIREX 1 mg/ml injection solution is supplied in clear glass vials packaged in boxes of 1 vial with a 1 ml fill volume for single-use, or 1 vial with a 4 ml fill volume for multi-use.

6.6 Special precautions for disposal

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

7 MEDICINE SCHEDULE

Prescripton Only Medicine

8 SPONSOR

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9 DATE OF FIRST APPROVAL

19 August 2010

10 DATE OF REVISION OF THE TEXT

31 January 2022

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.4	Data on serotonin syndrome removed
4.5	Data on serotonin syndrome removed
4.6	Fertility data included
4.8	Adverse event data updated
4.9	Poison Centre contact details added
5.2	Section updated
5.3	Section update
8	Sponsor address updated