

**Public Assessment Report**  
**Ondansetron 4mg/5ml Syrup**  
**Ondansetron hydrochloride dihydrate**  
**PL 20046/0036**  
**Focus Pharmaceuticals Ltd**

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## Lay Summary

The UK granted a marketing authorisation (licence) to Focus Pharmaceuticals Ltd for the medicinal product Ondansetron 4mg/5ml Syrup on 20/2/2008. The product is used to treat sickness and nausea caused by cancer treatment (chemotherapy and radiotherapy) and sickness and nausea after an operative procedure. The active ingredient is ondansetron hydrochloride dihydrate. The product is a prescription only medicine.

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Ondansetron 4mg/5ml Syrup outweigh the risks, hence a marketing authorisation was granted.

## Scientific Discussion

### INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted a marketing authorisation for the medicinal product Ondansetron 4mg/5ml Syrup (PL 20046/0036) on 20/02/2008. This was an abridged application according to Article 10.1 of Directive 2001/83/EC, claiming that the product was a generic medical product of Zofran Syrup, currently authorised to Glaxo Wellcome UK Limited as PL 10949/0246 (September 1996).

The active ingredient is ondansetron hydrochloride dihydrate and the product is indicated for the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy, and for the prevention of post-operative nausea and vomiting in adults. It is a prescription only medicine.

## PHARMACEUTICAL ASSESSMENT

### DRUG SUBSTANCE

#### Nomenclature

rINN: Ondansetron hydrochloride

Ph Eur name: Ondansetron hydrochloride dihydrate

USP name: Ondansetron hydrochloride

(3RS)-9-Methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-1,2,3,9-tetrahydro-4H-carbazol-4-one hydrochloride dihydrate

(±)-4-H-carbazol-4-one, 1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-monohydrochloride dihydrate

(±)-2,3-Dihydro-9-methyl-3-[(2-methylimidazol-1-yl)methyl]-carbazol-4(1H)-one monohydrochloride dihydrate

#### Structure

$C_{18}H_{19}N_3O \cdot HCl \cdot 2H_2O$

MW: 365.86

#### General Properties

Ondansetron hydrochloride dihydrate is a white to off-white crystalline powder sparingly soluble in water and alcohol, soluble in methanol, slightly soluble in dichloromethane, very slightly soluble in acetone, chloroform and in ethyl acetate.

Solubility in water is 3.2% and 0.8% in 0.9% saline. The pH of an aqueous 1% w/v solution is approximately 4.6. The pKa is 7.4 such that free base precipitates when the

pH is above the range 5.7-7.

An appropriate specification based on the European Pharmacopoeia has been provided.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Active ondansetron is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.

Batch analysis data are provided and comply with the proposed specification.

Satisfactory certificates of analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer during validation studies.

Appropriate stability data have been generated supporting.

## **DRUG PRODUCT**

### **Other ingredients**

The other ingredients are listed below, appropriate justification for the inclusion of each excipient has been provided.

- Citric acid anhydrous
- Sodium citrate dihydrate
- Sodium benzoate
- Sorbitol solution 70%
- Strawberry flavour (contains propylene glycol and ethanol)
- Purified water

All excipients are tested for compliance with the current relevant Ph Eur monographs with the exception of the strawberry flavour that is tested for compliance with an in-house specification. Specifications and Certificates of Analysis have been provided for all ingredients used in manufacture of the products. No materials of animal or human origin are used in the manufacture of the product. Satisfactory declarations have been provided from the suppliers.

### **Dissolution and impurity profiles**

Impurity profiles for the drug product were found to be similar to those for the reference product. The product is an oral solution and does not require dissolution profiles.

### **Manufacture**

A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Satisfactory process validation has been carried out.

**Finished product specification**

The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

**Container Closure System**

The product is presented in 70ml (nominal capacity) amber Type 3 glass bottles containing 50ml syrup sealed with tamper-evident aluminium lids containing polyethylene sealing discs. Satisfactory supplier and finished product manufacturer specifications and Certificates of Analysis have been provided for examples of the packaging components.

**Stability**

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 3 years has been set, which is satisfactory. Storage conditions are “Once opened use within 6 days”.

**ASSESSOR’S OVERALL CONCLUSIONS ON QUALITY AND ADVICE**

A Marketing Authorisation was granted.

## PRE-CLINICAL ASSESSMENT

Ondansetron hydrochloride, a carbazole, is a selective inhibitor of type 3 serotonin (5-hydroxytryptamine) receptors (5-HT<sub>3</sub>) that exhibits anti-emetic activity. The product is a syrup for oral consumption containing 4 mg ondansetron per 5 ml. It is intended for the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy, and for the prevention of post-operative nausea and vomiting in adults. The recommended dose is 8 mg one to two hours before chemotherapy or radiotherapy, followed by 8 mg twelve hours later, equivalent to a maximum of 0.32 mg/kg per day in a 50 kg human. To protect against delayed or prolonged emesis, treatment should be continued for up to five days at a rate of 8mg twice daily.

The applicant has provided a Nonclinical Overview which is satisfactory and written by a suitably qualified person. No new pre-clinical studies have been conducted.

The excipients are all commonly used and are listed in European Pharmacopoeial monographs, with the exception of strawberry flavouring, which is controlled by in-house specifications.

The impurities and residual solvents are controlled at acceptable limits.

This application has not revealed any evidence of untoward toxicity from treatment with Ondansetron 4 mg/5 ml syrup, beyond the already well-described effects of ondansetron and adequate warnings are proposed. A marketing authorisation may be granted.

## MEDICAL ASSESSMENT

### General

Ondansetron is a potent, highly selective 5HT<sub>3</sub> receptor-antagonist. Its precise mode of action in the control of nausea and vomiting is not known. Chemotherapeutic agents and radiotherapy may cause release of 5HT in the small intestine initiating a vomiting reflex by activating vagal afferents via 5HT<sub>3</sub> receptors. Ondansetron blocks the initiation of this reflex. Activation of vagal afferents may also cause a release of 5HT in the area postrema, located on the floor of the fourth ventricle, and this may also promote emesis through a central mechanism. Thus, the effect of ondansetron in the management of the nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy is probably due to antagonism of 5HT<sub>3</sub> receptors on neurons located both in the peripheral and central nervous system.

### Clinical Pharmacology

No formal data are presented and none are required for this application. As the preparation is a syrup, no bioequivalence study is required. The clinical expert provided a satisfactory overview of the PK and PD of ondansetron.

### Efficacy and Safety

No formal data are presented and none are required. The clinical expert provided a satisfactory overview of the efficacy and safety of ondansetron, in all relevant patient populations.

### Summary of Product Characteristics and Patient Information Leaflet

These are satisfactory.

### Conclusion

A Marketing Authorisation may be granted.

## **Overall Conclusion and Risk/Benefit Analysis**

### ***Quality***

The important quality characteristics of Ondansetron 4mg/5ml Syrup are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

### ***Pre-Clinical***

The pre-clinical expert report was satisfactory. No new preclinical data were submitted and none were required for applications of this type.

### ***Clinical***

No bioequivalence data presented or required as the product is an oral solution. A satisfactory expert report was provided with acceptable product literature.

### ***Risk/Benefit Analysis***

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. A market authorisation may be granted.



**Steps Taken During Assessment**

1	The MHRA received the application on 29/07/2004.
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 31/08/2004.
3	Following assessment of the application the MHRA requested further information from the applicant regarding the quality assessment on 08/04/2005 and 06/08/2007.
4	The applicant provided further information in regard to the quality assessment on 12/03/2007 and 02/11/2007.
5	The application was determined on 20/02/2008.

## **Steps Taken after Assessment**

No non-confidential changes have been made to the market authorisation.

## SUMMARY OF PRODUCT CHARACTERISTICS

### 1 NAME OF THE MEDICINAL PRODUCT

Ondansetron 4mg/5ml Syrup

### 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5ml contains 4mg of ondansetron as the hydrochloride dihydrate. The formulation also contains sorbitol.

For a full list of excipients, see section 6.1

### 3 PHARMACEUTICAL FORM

Syrup.

Clear strawberry flavoured liquid.

### 4 CLINICAL PARTICULARS

#### 4.1 Therapeutic indications

The management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy, and for the prevention of post-operative nausea and vomiting in adults.

#### 4.2 Posology and method of administration

*Chemotherapy and radiotherapy induced nausea and vomiting*

##### **Adults (including the elderly):**

The emetogenic potential of cancer treatment varies according to the doses and combinations of chemotherapy and radiotherapy regimens used. The route of administration and dose of Ondansetron should be flexible and selected as shown below.

*Emetogenic chemotherapy and radiotherapy:* Ondansetron can be given either by rectal, oral (tablets or syrup), intravenous or intramuscular administration. For oral administration: 8mg 1-2 hours before treatment, followed by 8mg 12 hours later.

To protect against delayed or prolonged emesis after the first 24 hours, oral or rectal treatment with Ondansetron should be continued for up to 5 days after a course of treatment. The recommended dose for oral administration is 8mg twice daily.

*Highly emetogenic chemotherapy (e.g high dose cisplatin):* Ondansetron can be given either by rectal, intravenous or intramuscular administration.

To protect against delayed or prolonged emesis after the first 24 hours, oral or rectal treatment with Ondansetron should be continued for up to 5 days after a course of treatment. The recommended dose for oral administration is 8mg twice daily.

##### **Children:**

Ondansetron may be administered as a single intravenous dose of 5mg/m<sup>2</sup> immediately before chemotherapy, followed by 4mg orally twelve hours later.

4mg orally twice daily should be continued for up to 5 days after a course of treatment.

*Post operative nausea and vomiting (PONV).*

**Adults:**

*For the prevention of PONV:* Ondansetron can be administered orally or by intravenous or intramuscular injection.

For oral administration: 16mg one hour prior to anaesthesia. Alternatively, 8mg one hour prior to anaesthesia followed by two further doses of 8mg at eight hourly intervals.

*For the treatment of established PONV:* Intravenous or intramuscular administration is recommended.

**Children (aged 2 years and over):**

*For the prevention and treatment of PONV:* Slow intravenous injection is recommended.

**Elderly:**

There is limited experience in the use of Ondansetron in the prevention and treatment of PONV in the elderly, however Ondansetron is well tolerated in patients over 65 years receiving chemotherapy.

*For both indications*

**Patients with renal impairment:**

No special requirements.

**Patients with hepatic impairment:**

Clearance of Ondansetron is significantly reduced and serum half life significantly prolonged in subjects with moderate or severe impairment of hepatic function. In such patients a total daily dose of 8mg should not be exceeded.

**Patients with poor sparteine/debrisoquine metabolism:**

The elimination half-life of ondansetron is not altered in subjects classified as poor metabolisers of sparteine and debrisoquine. Consequently in such patients repeat dosing will give drug exposure levels no different from those of the general population. No alteration of daily dosage or frequency of dosing are required.

**Route of administration**

Oral

**4.3 Contraindications**

Hypersensitivity to any ingredient of the formulation.

**4.4 Special warnings and precautions for use**

Hypersensitivity reactions have been reported in patients who have exhibited hypersensitivity to other selective 5HT<sub>3</sub> receptor antagonists.

Very rarely and predominantly with intravenous Ondansetron, transient ECG changes including QT interval prolongation have been reported. Therefore caution should be exercised in patients with cardiac rhythm or conduction disturbances, in patients treated with anti-arrhythmic agents or beta-adrenergic blocking agents and in patients with significant electrolyte disturbances.

As ondansetron is known to increase large bowel transit time, patients with signs of subacute intestinal obstruction should be monitored following administration.

Ondansetron syrup contains sorbitol and therefore patients with rare hereditary problems of fructose intolerance should not take this medicine.

#### 4.5 **Interaction with other medicinal products and other forms of interaction**

There is no evidence that ondansetron either induces or inhibits the metabolism of other drugs commonly co-administered with it. Specific studies have shown that ondansetron does not interact with alcohol, temazepam, furosemide, tramadol and propofol.

Ondansetron is metabolised by multiple hepatic cytochrome P-450 enzymes: CYP3A4, CYP2D6 and CYP1A2. Due to the multiplicity of metabolic enzymes capable of metabolising ondansetron, enzyme inhibition or reduced activity of one enzyme (e.g. CYP2D6 genetic deficiency) is normally compensated by other enzymes and should result in little or no significant change in overall ondansetron clearance or dose requirement.

*Phenytoin, Carbamazepine and Rifampicin:* In patients treated with potent inducers of CYP3A4 (i.e. Phenytoin, Carbamazepine and Rifampicin), the oral clearance of ondansetron was increased and ondansetron blood concentrations were decreased.

#### 4.6 **Pregnancy and lactation**

The safety of ondansetron for use in human pregnancy has not been established. Evaluation of experimental animal studies does not indicate direct or indirect harmful effects with respect to the development of the embryo, or foetus, the course of gestation and peri- and post-natal development. However as animal studies are not always predictive of human response the use of ondansetron in pregnancy is not recommended. Tests have shown that ondansetron passes into the milk of lactating animals. It is therefore recommended that mothers receiving Ondansetron should not breast-feed their babies.

#### 4.7 **Effects on ability to drive and use machines**

None reported

#### 4.8 **Undesirable effects**

Adverse events are listed below by system organ class and frequency. Frequencies are defined as: very common ( $\geq 1/10$ ), common ( $\geq 1/100$  and  $< 1/10$ ), uncommon ( $\geq 1/1000$  and  $< 1/100$ ), rare ( $\geq 1/10,000$  and  $< 1/1000$ ) and very rare ( $< 1/10,000$ ) including isolated reports. Very common, common and uncommon events were generally determined from clinical trial data. The incidence in placebo was taken into account. Rare and very rare events were generally determined from post-marketing spontaneous data.

The following frequencies are estimated at the standard recommended doses of ondansetron according to indication and formulation.

Immune system disorders

Rare: Immediate hypersensitivity reactions sometimes severe, including anaphylaxis.

#### Nervous system disorders

Very common: Headache.

Uncommon: Seizures, movement disorders including extrapyramidal reactions such as dystonic reactions, oculogyric crisis and dyskinesia have been observed without definitive evidence of persistent clinical sequelae.

#### Cardiac disorders

Uncommon: Arrhythmias, chest pain with or without ST segment depression, bradycardia.

#### Vascular disorders

Common: Sensation of warmth or flushing.

Uncommon: Hypotension.

#### Respiratory, thoracic and mediastinal disorders

Uncommon: Hiccups.

#### Gastrointestinal disorders

Common: Constipation.

#### Hepatobiliary disorders

Uncommon: Asymptomatic increases in liver function tests<sup>#</sup>.

<sup>#</sup>These events were observed commonly in patients receiving chemotherapy with cisplatin.

### 4.9 Overdose

Little is known at present about overdosage with ondansetron, however, a limited number of patients received overdoses. Manifestations that have been reported include visual disturbances, severe constipation, hypotension and a vasovagal episode with transient second degree AV block. In all instances, the events resolved completely. There is no specific antidote for ondansetron, therefore in all cases of suspected overdose, symptomatic and supportive therapy should be given as appropriate.

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Ondansetron is a potent, highly selective 5HT<sub>3</sub> receptor-antagonist. Its precise mode of action in the control of nausea and vomiting is not known. Chemotherapeutic agents and radiotherapy may cause release of 5HT in the small intestine initiating a vomiting reflex by activating vagal afferents via 5HT<sub>3</sub> receptors. Ondansetron blocks the initiation of this reflex. Activation of vagal afferents may also cause a release of 5HT in the area postrema, located on the floor of the fourth ventricle, and this may also promote emesis through a central mechanism. Thus, the effect of ondansetron in the management of the nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy is probably due to antagonism of 5HT<sub>3</sub> receptors on neurons located both in the peripheral and central nervous system. The mechanisms of

action in postoperative nausea and vomiting are not known but there may be common pathways with cytotoxic induced nausea and vomiting. Ondansetron does not alter plasma prolactin concentrations. The role of ondansetron in opiate-induced emesis is not yet established.

## 5.2 Pharmacokinetic properties

Following oral administration, ondansetron is passively and completely absorbed from the gastrointestinal tract and undergoes first pass metabolism. Peak plasma concentrations of about 30ng/ml are attained approximately 1.5 hours after an 8mg dose. For doses above 8mg the increase in ondansetron systemic exposure with dose is greater than proportional; this may reflect some reduction in first pass metabolism at higher oral doses. Bioavailability, following oral administration, is slightly enhanced by the presence of food but unaffected by antacids. Studies in healthy elderly volunteers have shown slight, but clinically insignificant, age-related increases in both oral bioavailability (65%) and half-life (5 hours) of ondansetron. Gender differences were shown in the disposition of ondansetron, with females having a greater rate and extent of absorption following an oral dose and reduced systemic clearance and volume of distribution (adjusted for weight). The disposition of ondansetron following oral, intramuscular(IM) and intravenous(IV) dosing is similar with a terminal half life of about 3 hours and steady state volume of distribution of about 140L. Equivalent systemic exposure is achieved after IM and IV administration of ondansetron. A 4mg intravenous infusion of ondansetron given over 5 minutes results in peak plasma concentrations of about 65ng/ml. Following intramuscular administration of ondansetron, peak plasma concentrations of about 25ng/ml are attained within 10 minutes of injection.

Following administration of ondansetron suppository, plasma ondansetron concentrations become detectable between 15 and 60 minutes after dosing. Concentrations rise in an essentially linear fashion, until peak concentrations of 20-30 ng/ml are attained, typically 6 hours after dosing. Plasma concentrations then fall, but at a slower rate than observed following oral dosing due to continued absorption of ondansetron. The absolute bioavailability of ondansetron from the suppository is approximately 60% and is not affected by gender. The half life of the elimination phase following suppository administration is determined by the rate of ondansetron absorption, not systemic clearance and is approximately 6 hours. Females show a small, clinically insignificant, increase in half-life in comparison with males.

Ondansetron is not highly protein bound (70-76%). Ondansetron is cleared from the systemic circulation predominantly by hepatic metabolism through multiple enzymatic pathways. Less than 5% of the absorbed dose is excreted unchanged in the urine. The absence of the enzyme CYP2D6 (the debrisoquine polymorphism) has no effect on ondansetron's pharmacokinetics. The pharmacokinetic properties of ondansetron are unchanged on repeat dosing.

In a study of 21 paediatric patients aged between 3 and 12 years undergoing elective surgery with general anaesthesia, the absolute values for both the clearance and volume of distribution of ondansetron following a single intravenous dose of 2mg (3-7 years old) or 4mg (8-12 years old) were reduced.

The magnitude of the change was age-related, with clearance falling from about 300mL/min at 12 years of age to 100mL/min at 3 years. Volume of distribution fell from about 75L at 12 years to 17L at 3 years. Use of weight-based dosing (0.1mg/kg up to 4mg maximum) compensates for these changes and is effective in normalising systemic exposure in paediatric patients.

In patients with renal impairment (creatinine clearance 15-60 ml/min), both systemic clearance and volume of distribution are reduced following IV administration of ondansetron, resulting in a slight, but clinically insignificant, increase in elimination half-life (5.4h). A study in patients with severe renal impairment who required regular haemodialysis (studied between dialyses) showed ondansetron's pharmacokinetics to be essentially unchanged following IV administration.

Specific studies in the elderly or patients with renal impairment have been limited to IV and oral administration. However, it is anticipated that the half-life of ondansetron after rectal administration in these populations will be similar to that seen in healthy volunteers, since the rate of elimination of ondansetron following rectal administration is not determined by systemic clearance.

Following oral, intravenous or intramuscular dosing in patients with severe hepatic impairment, ondansetron's systemic clearance is markedly reduced with prolonged elimination half-lives (15-32 h) and an oral bioavailability approaching 100% due to reduced pre-systemic metabolism. The pharmacokinetics of ondansetron following administration as a suppository have not been evaluated in patients with hepatic impairment.

### **5.3 Preclinical safety data**

No additional data of relevance.

## **6 PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Citric acid anhydrous

Sodium citrate dihydrate

Sodium benzoate

Sorbitol solution 70%

Strawberry flavour (contains propylene glycol and ethanol)

Purified water

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

3 years unopened.

Once opened use within 6 days.

### **6.4 Special precautions for storage**

No special requirements.



**6.5 Nature and contents of container**  
75ml type III amber glass bottle with a tamper evident aluminium cap with an EPE liner containing 50ml.

**6.6 Special precautions for disposal**  
No special requirements.

**7 MARKETING AUTHORISATION HOLDER**

Focus Pharmaceuticals Ltd  
Unit 5, Faraday Court  
Centrum 100  
First Avenue  
Burton-upon-Trent  
Staffs, DE14 2WX

**8 MARKETING AUTHORISATION NUMBER(S)**

PL 20046/0036

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

20/02/2008

**10 DATE OF REVISION OF THE TEXT**

20/02/2008

## Leaflet and Labelling

Package Leaflet

# Ondansetron 4mg/5ml Syrup

(Ondansetron)

# FOCUS

Read this leaflet carefully before you start taking this medicine.

Keep this leaflet; you may need to read it again. If you have any further questions or you are not sure about anything, ask your doctor or pharmacist. This medicine is for you personally and should not be given to anyone else. It may harm them, even if their symptoms are the same as yours.

### About your medicine

Your medicine is called Ondansetron Syrup.

It is part of a group of drugs known as 5HT<sub>3</sub> receptor antagonists or anti-emetics.

### What is in your medicine?

Each 5ml of Ondansetron Syrup contains 4 milligrams (mg) of the active ingredient ondansetron as the hydrochloride dihydrate salt. The inactive ingredients are citric acid anhydrous, sodium citrate dihydrate, sodium benzoate, sorbitol liquid 70%, strawberry flavour (containing propylene glycol and ethanol) and purified water.

The liquid is clear and colourless. It comes in glass bottles containing 50ml.

### Who makes your medicine?

Your syrup is made by Vianex SA, 12<sup>th</sup> Km. Athens-Lamia National Road, 144 51 Metamorphossi Athens, Greece.

The marketing authorisation holder is Focus Pharmaceuticals Ltd, Unit 5, Faraday Court, Burton-upon-Trent, Staffs., DE14 2WX, UK.

### What is your medicine used for?

Ondansetron is used to manage sickness and vomiting as a result of chemotherapy, radiotherapy or after an operation.

### Before you take your medicine

Tell your doctor before you start to take your medicine if:

- ❑ you have ever had a bad reaction to any of the ingredients listed in the 'What is in your medicine' section or another 5HT<sub>3</sub> receptor antagonist;
- ❑ you are pregnant, may become pregnant or are breast-feeding;
- ❑ you have ever had any problems with your liver;
- ❑ you have a blockage in your gut or bowel or suffer from constipation;
- ❑ you have problems with your heart;
- ❑ the amount of sodium, potassium or chloride in your body is very low or very high.

### Using other medicines

Make sure your doctor knows if you are taking a medicine listed here:

- ❑ beta blockers such as atenolol to treat high blood pressure or angina (pains in your chest): use with ondansetron may cause a change to your heart rate.
- ❑ Anti-arrhythmics such as amiodorone to control your heart rate: use with ondansetron may cause a change to your heart rate.
- ❑ Phenytoin and carbamazepine to treat epilepsy, or rifampicin to treat tuberculosis; ondansetron may not work as well when taken with any of these medicines.

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

### Important information about some of the ingredients in Ondansetron Syrup

- ❑ Your medicine contains sorbitol. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.
- ❑ Your medicine contains a very small amount of alcohol, less than 100mg per dose. This should not affect you.

### How to take your medicine

#### Use during and after chemotherapy and radiotherapy

The usual adult dose is 10ml (8mg) one to two hours before treatment, then a further 10ml (8mg) twelve hours later. Your treatment may continue for up to five days after therapy with a dose of 10ml (8mg) twice a day.

The usual dose for children is 5ml (4mg) twelve hours after chemotherapy or radiotherapy. Your child's treatment may continue for up to five days after therapy with a dose of 5ml (4mg) twice a day

#### After an operation

The usual adult dose is 20ml (16mg) one hour prior to your operation or 10ml (8mg) one hour prior to your operation followed by 10ml (8mg) eight and 10ml (8mg) sixteen hours after your operation.

The use of ondansetron is not recommended for children undergoing an operation.

If you have problems with your liver your dose must not exceed 10ml (8mg) per day.

### If you forget to take a dose

If you forget to take a dose at the right time, take it as soon as you remember. Do not take two doses together. If it is almost time to take the next dose, wait until then and then carry on as before.

### If you take more Ondansetron Syrup than you should

Contact the nearest hospital casualty department or a doctor for advice if you have swallowed too much liquid or if you think a child has accidentally swallowed any.

Take this leaflet and any Ondansetron Syrup that you still have to show the doctor.

### Possible side effects

Very rarely someone may be allergic to Ondansetron syrup. If you have any of the side effects listed below then you must stop taking Ondansetron syrup and tell your doctor **immediately**:

- sudden wheeziness or tightness of the chest
- difficulty breathing
- swelling of the face, lips or eyelids
- a lumpy rash (hives) anywhere on the body
- unexplained fever
- feeling faint, especially when standing up.

The following side effects are very common (more than 1 person in 10):

- headache.

The following side effects are common (more than 1 person in 100 but less than 1 person in 10):

- constipation;
- flushing or feeling warm.

The following side effects are uncommon (more than 1 person in 1000 but less than 1 person in 100):

- seizures;
- chest pains;
- irregular or slow heartbeat or low blood pressure making you feel giddy or light headed;
- muscle weakness, problems controlling movement or problems with the movement in your eyes;
- Hiccups.

The following side effects are rare:

- Chest pain;
- Involuntary movements.

If you need a blood test tell your doctor you are taking this medicine as it may affect the results of liver function tests. This effect is more commonly seen if you are on chemotherapy with cisplatin.

### Storing your medicine

Keep your medicine in a safe place where children cannot see or reach it.

Ondansetron Syrup does not require any special storage conditions.

Do not use unopened bottles of Ondansetron Syrup after the

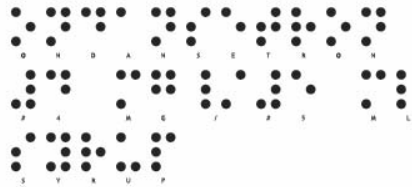
'expiry' date printed on the label and the carton.

Once you have opened the bottle, use within six days.

This leaflet was prepared in October 2007

FOCUS

<p style="text-align: right;">50ml</p> <p style="text-align: center;"><b>Ondansetron 4mg/5ml Syrup</b></p>	<p><b>Ondansetron 4mg/5ml Syrup</b></p> <p style="text-align: center;"><b>4mg/5ml</b></p> <p>Each 5ml of Syrup contains 4mg ondansetron as hydrochloride dihydrate. It also contains sorbitol, liquid (non-crystallising).</p> <p>To be taken by mouth. Use only as directed by a doctor. Read the enclosed Patient Information Leaflet before taking your medicine. Once open use within 6 days. <b>Keep out of the reach and sight of children.</b></p> <p style="text-align: right;"><b>POM</b></p> <p style="writing-mode: vertical-rl; transform: rotate(180deg);"><b>Focus Pharmaceuticals Ltd</b></p>	<p><b>Ondansetron 4mg/5ml Syrup</b></p>  <p style="text-align: right;"><b>POM</b></p> <p style="writing-mode: vertical-rl; transform: rotate(180deg);"><b>Focus Pharmaceuticals Ltd</b></p>	<p><b>Ondansetron 4mg/5ml Syrup</b></p> <p style="text-align: center;"><b>4mg/5ml</b></p> <div style="border: 1px solid black; width: 100%; height: 20px; margin-bottom: 10px;"></div> <p>Date bottle opened</p>  <p>5 060064 790489</p> <p>PL 20046/0036</p> <p>PL Holder: Focus Pharmaceuticals Ltd Unit 5 · Faraday Court Centrum 100 · First Avenue Burton-upon-Trent Staffs DE14 2WX</p>
<p>50ml</p> <p style="text-align: center;"><b>FOCUS</b></p>	<p style="text-align: center;"><b>FOCUS</b></p>	<p>50ml</p> <p style="text-align: center;"><b>FOCUS</b></p> <p style="writing-mode: vertical-rl; transform: rotate(180deg);"><b>Focus Pharmaceuticals Ltd</b></p>	<p>Batch No</p> <p>Exp</p>



<p><b>Ondansetron 4mg/5ml Syrup</b></p> <p style="text-align: right;"><b>POM</b></p> <p>PL 20046/0036</p> <p>50ml</p>	<p>Each 5ml of liquid contains 4mg ondansetron as hydrochloride dihydrate. It also contains sorbitol, liquid (non-crystallising). To be taken by mouth. Use only as directed by a doctor. Read the enclosed Patient Information Leaflet before taking your medicine. Once open use within 6 days. <b>Keep out of reach and sight of children.</b></p> <p>PL Holder: Focus Pharmaceuticals Ltd Unit 5, Faraday Court, Centrum 100, First Avenue Burton-upon-Trent, Staffs DE14 2WX</p>	<div style="border: 1px solid black; width: 100%; height: 20px; margin-bottom: 5px;"></div> <p>BN EXP</p> <p style="writing-mode: vertical-rl; transform: rotate(180deg);"><b>Focus Pharmaceuticals Ltd</b></p>
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