



## Public Assessment Report

from the Norwegian Medicines Agency

Ondansetron Copyfarm film-coated tablets 4 mg and 8 mg  
ondansetron

Copyfarm AS, Danmark

MA-numbers in Norway: 04-2964, 04-2965

**Date: 2008-06-10**

This assessment report is published by the Norwegian Medicines Agency (NoMA) following Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier which was submitted to the NoMA and its fellow organisations in all concerned EEA member states. It reflects the scientific discussion between the NoMA and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval and issue of a marketing authorisation.

This assessment report will be updated by an addendum whenever new important information becomes available.

Module 1: Information about the initial procedure

Module 2: Summary of product Characteristics (SPC)

Module 3: Package Leaflet

Module 4: Labelling

Module 5: Scientific discussion

Module 6: Update

## **Module 1: Information about the initial procedure:**

1. Type of application: Abridged application according to Directive 2001/83/EC as amended, Article 10(1) generic application, claiming essential similarity.
2. Active substance: ondansetron
3. Pharmaceutical form: film-coated tablets
4. Strength: 4 mg and 8 mg
5. MA holder: Copyfarm AS, Odense S, Denmark
6. Reference Member State: Norway
7. Concerned Member States: Finland, Germany and Sweden
8. Procedure-number: : NO/H/0133/001-002/MR
9. Timetable:  
Start (Day 0): 05.12.2007  
End (Day 90): 04.03.2008

## Module 2: Summary of product Characteristics (SPC)

### 1. NAME OF THE MEDICINAL PRODUCT

Ondansetron Copyfarm 4 mg film-coated tablets  
Ondansetron Copyfarm 8 mg film-coated tablets

### 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains: Ondansetron hydrochloride dihydrate equivalent to 4 mg and 8 mg ondansetron, respectively.

Excipient(s): Lactose

For a full list of excipients, see section 6.1.

### 3. PHARMACEUTICAL FORM

Film-coated tablets.

Ondansetron 4 mg is a yellow, oval, biconvex, film-coated tablet embossed with 'BL' on one side and 4 on the other side.

Ondansetron 8 mg is a yellow, oval, biconvex, film-coated tablet embossed with 'BL' on one side and 8 on the other side.

### 4. CLINICAL PARTICULARS

#### 4.1 Therapeutic indications

Ondansetron is indicated for the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy, and for the prevention and treatment of post-operative nausea and vomiting.

#### 4.2 Posology and method of administration

Oral use.

For the different dosage regimens appropriate strengths and formulations are available.

##### Chemotherapy and radiotherapy induced nausea and vomiting

###### Adults

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

For patients receiving emetogenic chemotherapy or radiotherapy ondansetron can be given either by oral or intravenous administration.

For most patients receiving emetogenic chemotherapy or radiotherapy, ondansetron should initially be administered intravenously immediately before treatment, followed by 8 mg orally twelve hourly.

For oral administration: 8 mg 1-2 hours before treatment, followed by 8 mg 12 hours later.

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

#### Highly emetogenic chemotherapy

For patients receiving highly emetogenic chemotherapy, e.g. high-dose cisplatin, ondansetron can be given by intravenous administration.

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

#### Children (aged 2 years and over) and adolescents (< 18 years)

Experience in paediatric patients is limited. In children older than two years, ondansetron may be administered as a single intravenous dose of 5 mg/m<sup>2</sup> over 15 minutes immediately before chemotherapy, followed by 4 mg orally twelve hours later. Oral treatment with a dose according to the body area should be continued for up to 5 days after a course of treatment. Children with a total body area between 0.6 and 1.2 m<sup>2</sup> should receive a dosage schedule of 4 mg 2 times a day, while children with a body area above 1.2 m<sup>2</sup> should receive 8 mg 2 times a day.

There is no experience in children younger than 2 years old.

Ondansetron film-coated tablets cannot be used in children with a total body surface below 0.6 m<sup>2</sup>.

#### Elderly

Ondansetron is well tolerated by patients over 65 years and no alteration of dosage, dosing frequency or route of administration are required.

Please refer also to "Special populations".

#### Post-operative nausea and vomiting

##### Adults

Prevention of post-operative nausea and vomiting

For the prevention of post-operative nausea and vomiting ondansetron can be administered orally or by intravenous injection.

For oral administration:

16 mg one hour prior to anaesthesia.

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

#### Treatment of established post-operative nausea and vomiting

For the treatment of established post-operative nausea and vomiting intravenous administration is recommended.

#### Children (aged 2 years and over) and adolescents (< 18 years)

For the prevention and treatment of post-operative nausea and vomiting slow intravenous injection is recommended.

#### Elderly

There is limited experience in the use of ondansetron in the prevention and treatment of post-operative nausea and vomiting in the elderly, however ondansetron is well tolerated in patients over 65 years receiving chemotherapy.

Please refer also to "Special populations".

#### Special populations

##### Patients with renal impairment

No alteration of daily dosage or frequency of dosing, or route of administration are required.

##### 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 8 mg 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 medicinal product exposure levels no different from those of the general population. No alteration of daily dosage or frequency of dosing are required.

### **4.3 Contraindications**

Hypersensitivity to ondansetron or to other selective 5-HT<sub>3</sub>-receptor antagonists (e.g. granisetron, dolasetron) or to any of the excipients.

### **4.4 Special warnings and precautions for use**

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

In patients with adenotonsillar surgery prevention of nausea and vomiting with ondansetron may mask occult bleeding. Therefore, such patients should be followed carefully after ondansetron.

Since there is little experience to date of the use of ondansetron in cardiac patients, caution should be exercised if ondansetron is coadministered with anaesthetics to patients with arrhythmias or cardiac conduction disorders or to patients who are being treated with antiarrhythmic agents or beta-blockers.

Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Ondansetron film-coated tablets should not be used in children with a total body surface below 0.6 m<sup>2</sup>.

The medicinal product should not be used for children younger than two years, as for these patients the experience is limited.

#### **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 medicinal products commonly coadministered with it. Specific studies have shown that ondansetron does not interact with alcohol, temazepam, furosemide, alfentanil, propofol and thiopental.

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.

*Tramadol:* Data from small studies indicate that ondansetron may reduce the analgesic effect of tramadol.

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

##### *Pregnancy*

Use in pregnancy has not been established and is not recommended.

Data on a limited number of exposed pregnancies indicate no adverse effects of ondansetron on pregnancy or on the health of the foetus/newborn child. To date, no other relevant epidemiological data are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. Use in human pregnancy has not been established and is not recommended. If it is absolutely necessary that Ondansetron is given caution should be exercised when prescribing to pregnant women especially in the first trimester. A careful risk/benefit assessment should be performed.

##### *Lactation*

Tests have shown that ondansetron passes into the milk of lactating animals (see section 5.3). It is therefore recommended that mothers receiving ondansetron should not breast-feed their babies.

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

Ondansetron has no or negligible influence on the ability to drive and use machines..

#### **4.8 Undesirable effects**

The side effects are listed according to organ classes and frequency. Frequencies are defined as: very common (>1/10); common ( $\geq$ 1/100, <1/10); uncommon ( $\geq$ 1/1,000 and <1/100); rare ( $\geq$ 1/10,000 and <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

Very common, common and uncommon events were generally determined from clinical trial data. 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: Extrapyramidal reactions (such as oculogyric crisis/dystonic reactions) have been observed without definitive evidence of persistent clinical sequelae; seizures

*Rare*: Dizziness during rapid intravenous administration.

#### Eye disorders:

*Rare*: Transient visual disturbances (eg. blurred vision) predominantly during rapid intravenous administration.

*Very rare*: transient blindness predominantly during intravenous administration.

The majority of the blindness cases reported resolved within 20 minutes. Most patients had received chemotherapeutic agents, which included cisplatin. Some cases of transient blindness were reported as cortical in origin.

#### 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. These events were observed commonly in patients receiving chemotherapy with cisplatin).

#### General disorders and administration site conditions:

Common: Local intravenous injection site reactions.

## **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**

Pharmacotherapeutic group: Antiemetics and antinauseants, Serotonin (5-HT<sub>3</sub>) antagonists.

ATC code: A04AA01.

Ondansetron is a potent, highly selective 5-HT<sub>3</sub> receptor-antagonist.

Its precise antiemetic and antinauseal mechanism of action is not known. Chemotherapeutic agents and radiotherapy may cause release of 5-HT in the small intestine initiating a vomiting reflex by activating vagal afferents via 5-HT<sub>3</sub> receptors. Ondansetron blocks the initiation of this reflex. Activation of vagal afferents may also cause a release of 5-HT 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 5-HT<sub>3</sub> receptors on neurons located both in the peripheral and central nervous system. The mechanisms of action in post-operative nausea and vomiting are not known but there may be common pathways with cytotoxic induced nausea and vomiting.

In a pharmaco-psychological study in volunteers ondansetron has not shown a sedative effect.

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 (bioavailability is about 60%). Peak plasma concentrations of about 30 ng/ml are attained approximately 1.5 hours after an 8 mg dose. For doses above 8 mg 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 140 L. Equivalent systemic exposure is achieved after IM and IV administration of ondansetron.

The protein binding of ondansetron is 70-76%. A direct effect of plasma concentration and anti-emetic effect has not been established. 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 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 2 mg (3-7 years old) or 4 mg (8-12 years old) were reduced. The magnitude of the change was age-related, with clearance falling from about 300 ml/min at 12 years of age to 100ml/min 3 years. Volume of distribution fell from about 75 l at 12 years to 17 l at 3 years. Use of weight- based dosing (0.1 mg/kg up to 4 mg maximum) compensates for these changes and is effective in normalizing systemic exposure in paediatric patients.

In patients with moderate renal impairment (creatinine clearance 15-60ml/min), both systemic clearance and volume of distribution are reduced, 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 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.

### **5.3 Preclinical safety data**

Preclinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential.

Ondansetron and its metabolites accumulate in the milk of rats; milk/plasma-ratio was 5.2.

A study of cloned human cardiac ion channels has shown that ondansetron has the potential to affect cardiac repolarisation via blockade of HERG potassium channels. The clinical relevance of this finding is uncertain.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Lactose, anhydrous  
Cellulose, microcrystalline  
Maize starch, pregelatinised  
Magnesium stearate  
Hypromellose  
Titanium dioxide (E171)  
Iron oxide yellow (E172).

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

3 years.

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

This medicinal product does not require any special storage conditions.

### **6.5 Nature and contents of container**

4 mg blister (PVC/Al): 10, 14, 15, 28, 30, 50, 56, 98 and 100 film-coated tablets.  
8 mg blister (PVC/Al): 10, 14, 15, 28, 30, 50, 56, 98 and 100 film-coated tablets.

Not all pack sizes may be marketed.

### **6.6 Special precautions for disposal and other handling**

No special requirements.

## **7. MARKETING AUTHORISATION HOLDER**

## **8. MARKETING AUTHORISATION NUMBER(S)**

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

## **10. DATE OF REVISION OF THE TEXT**

2008-03-04

# **Module 3: Package Leaflet**

## **PACKAGE LEAFLET: INFORMATION FOR THE USER**

### **Ondansetron Copyfarm 4 mg and 8 mg film-coated tablets**

Ondansetron

#### **Read all of 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, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

#### **In this leaflet:**

1. What Ondansetron Copyfarm is and what it is used for
2. Before you take Ondansetron Copyfarm
3. How to take Ondansetron Copyfarm
4. Possible side effects
5. How to store Ondansetron Copyfarm
6. Further information

## **1. WHAT ONDANSETRON COPYFARM IS AND WHAT IT IS USED FOR**

Ondansetron Copyfarm belongs to a group of medicinal products called anti emetics. Ondansetron inhibits the effect of the neuro- transmitter serotonin in the brain. Serotonin causes nausea and vomiting.

Ondansetron is used to prevent or treat nausea and vomiting induced by chemotherapy or radiotherapy. In addition it may be used to prevent or treat post-operative nausea and vomiting.

Please note that your doctor may have prescribed the medicine for a different use and/or with a different dosing than mentioned in this leaflet. Always follow your doctor's instructions written on the label of the package.

## **2. BEFORE YOU TAKE ONDANSETRON COPYFARM**

### **Do not take Ondansetron Copyfarm**

- if you are allergic (hypersensitive) to ondansetron or any of the other ingredients in Ondansetron Copyfarm.(see 6 Further information).
- if you are hypersensitive to other medicinal products belonging to the group of selective serotonin (5-HT<sub>3</sub>)-receptor antagonists (e.g. granisetron, dolasetron). It is, in such case, possible that you are also allergic to ondansetron.

#### **Take special care with Ondansetron Copyfarm**

- if you have stricture of intestines or constipation, because you will need special surveillance by your doctor.
- if you are going to have or recently have had your tonsils removed, because treatment with Ondansetron Copyfarm may hide symptoms of internal bleeding.
- if you are heart patient (with arrhythmias or conduction disorders) and are being treated with other medication such as anesthetics, anti-arrhythmics or beta-blockers at the same time, because of the limited experience hereby.
- if it is for children below the age of 2 years or with a body surface of less than 0.6 m<sup>2</sup>.
- if you have liver impairment.

Tell your doctor if any of the above warnings apply to you.

Always inform the laboratory during tests of blood and urine that you are being treated with Ondansetron Copyfarm.

#### **Taking other medicines**

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

It is important to inform your doctor if you are being treated with:

- epilepsy medicine (phenytoin, carbamazepine)
- a specific antibiotic (rifampicin)
- pain-relieving medicine (tramadol)

Contact your doctor. It may be necessary to adjust the dose.

#### **Taking Ondansetron Copyfarm with food and drink**

Ondansetron Copyfarm can be taken independently of meals.

#### **Pregnancy and breast-feeding**

Ask your doctor or pharmacist for advice before taking any medicine.

Pregnancy:

There is only limited experience with the use of Ondansetron Copyfarm during pregnancy. If you are pregnant, especially during the first third of your pregnancy, you should use Ondansetron Copyfarm only, if your doctor has told you to.

Breast-feeding:

You should not breast-feed your infant whilst taking Ondansetron Copyfarm.

#### **Driving and using machines**

Ondansetron Copyfarm does not affect the ability to use any tools or machines or the ability to drive safely in traffic.

#### **Important information about some of the ingredients of Ondansetron Copyfarm**

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

### **3. HOW TO TAKE ONDANSETRON COPYFARM**

Always take Ondansetron Copyfarm exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. The dose is always determined by your doctor who is adjusting the dose for you so you will achieve optimal effect.

If you feel that the effect of Ondansetron Copyfarm is too strong or too weak you should tell your doctor or pharmacist.

*Treatment and prevention of nausea and vomiting in connection with chemotherapy or radiotherapy*

**Adults:**

8 mg 1-2 hours before chemotherapy or radiotherapy, followed by 8 mg every 12 hours for up to 5 days. Your doctor may decide to give the first dose as an injection.

**Elderly:**

The same dose as for adults.

**Children (age 2 years and up) and adolescents under the age of 18 years:**

The dose is individual and depends on the size/surface of the child. Ondansetron Copyfarm should not be used for children with a total body surface of less than 0.6 m<sup>2</sup>.

*Treatment and prevention of post-operative nausea and vomiting.*

**Adults, prevention and treatment:**

16 mg one hour prior to anesthesia or alternatively, 8 mg administered one hour prior to anesthesia followed by an additional 8 mg after 8 and 16 hours. Your doctor may choose to give you the medicine as injections.

**Elderly, prevention and treatment:**

There is limited experience with the use of ondansetron to elderly patients. Ondansetron is however tolerated well by patients above 65 years in chemotherapy (please refer to sections above).

**Insufficient function of the liver:**

The daily dose should not exceed 8 mg if you have moderately to severely decreased function of the liver.

The tablets should be taken with a glass of water.

Always follow your doctor's prescription. There are differences in what the individual patients need. Changes in or discontinuation of treatment should only occur in consultation with your doctor.

**If you take more Ondansetron Copyfarm than you should**

There is limited experience with overdosage with Ondansetron Copyfarm. Contact your doctor, emergency room or pharmacist if you have taken more Ondansetron Copyfarm than stated in this leaflet or if a child accidentally has ingested the medicine. In case of other questions concerning the medicine ask your doctor or pharmacist. The symptoms of overdose are disturbances of vision, severe constipation, low blood pressure and disturbances in heart beat rhythm.

**If you forget to take Ondansetron Copyfarm**

Do not take a double dose to make up for a forgotten dose.

**4. POSSIBLE SIDE EFFECTS**

Like all medicines, Ondansetron Copyfarm can cause side effects, although not everybody gets them.

A few people can be allergic to some medicines. If any of the following happen, stop taking Ondansetron Copyfarm and tell your doctor immediately or go to the casualty department of the nearest hospital:

- Severe itching of the skin, rash
- Swelling of the hands, feet, ankles, face, lips, mouth or throat, which may cause difficulties in swallowing or breathing.
- Collapse

*Very common (occur in more than 1 of 10 treated).*  
Headache.

*Common (occur in between 1 and 10 of 100 treated).*  
A sensation of reddening and warmth. Constipation.

*Uncommon (occur in between 1 and 10 of 1.000 treated).*  
Seizures. Hiccups. Low blood pressure, irregular heart beats, heart pain and slow pulse. Involuntary movements. Involuntary eye movements. Sometimes changes in liver function have been observed.

*Rare (occur in between 1 and 10 of 10.000 treated).*  
Nettle rash (urticaria). Dizziness, transient blurred vision predominantly during intravenous administration.  
Anaphylactic shock collapse, including swollen tongue and throat and trouble with breathing.

*Very rare side effects (occur in less than 1 of 10.000 treated):*  
Transient blindness predominantly during intravenous administration. Most of these blindness cases were resolved within 20 minutes.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

## **5. HOW TO STORE Ondansetron Copyfarm**

Keep out of the reach and sight of children.

Do not use Ondansetron Copyfarm after the expiry date which is stated on the carton after EXP. The expiry date refers to the last day of that month.

This medicinal product does not require any special storage conditions.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

## **6. FURTHER INFORMATION**

### **What Ondansetron Copyfarm contains**

- The active substance is ondansetron hydrochloride dihydrate corresponding to 4 mg and 8 mg ondansetron, respectively.  
The other ingredients are: lactose, microcrystalline cellulose, pregelatinised maize starch, magnesium stearate, hypromellose, titanium dioxide (E171), yellow iron oxide (E172).

**What Ondansetron Copyfarm looks like and contents of the pack**

Ondansetron Copyfarm 4 mg is a yellow, oval, biconvex, film-coated tablet embossed with 'BL' on one side and 4 on the other side.

Ondansetron Copyfarm 8 mg is a yellow, oval, biconvex, film-coated tablet embossed with 'BL' on one side and 8 on the other side.

Pack sizes (PVC/Al blister):

10, 14, 15, 28, 30, 50, 56, 98 or 100 film-coated tablets.

Not all pack sizes may be marketed.

**Marketing Authorisation Holder:**

Copyfarm A/S  
Energivej 15  
DK-5260 Odense S  
Denmark

**Manufacturer**

Copyfarm A/S  
Energivej 15  
DK-5260 Odense S  
Denmark

**This leaflet was last approved in 2008-03-04**

**Module 4: Labelling**

Not included.

## Module 5: Scientific discussion

**This module reflects the scientific discussion for the approval of Ondansetron Copyfarm film-coated tablets 4 mg and 8 mg. The procedure was finalised at 2008-03-04 (on Day 90). For information on changes after this date please refer to the module 'Update'.**

### I. INTRODUCTION

Based on review of the submitted data, the Member States have granted a marketing authorisation (MA) for Ondansetron Copyfarm film-coated tablets 4 mg and 8 mg from Copyfarm A/S. The first date of authorisation in Norway was 20. November 2006. The product is indicated for the following indications:

Ondansetron is indicated for the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy, and for the prevention and treatment of post-operative nausea and vomiting

A comprehensive description of the indications and posology is given in the SPC (see Module 3).

The marketing authorisation in Norway is granted according to Directive 2001/83/EC as amended, Article 10(1) generic application.

This concerns a generic application claiming essential similarity to the innovator product Zofran «GlaxoSmithKline». Zofran film-coated tablets have been marketed in Norway since 06.07.1992. In addition, reference is also made to Zofran authorisations in the individual Member States (reference product). This type of application refers to information which is contained in the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the original authorised medicinal product, which is legally permitted once the data protection time of the dossier of the reference product and patent rights have expired. Usually, it is necessary to demonstrate that the generic product has the same pharmacokinetic profile as the originator. This has been demonstrated for Ondansetron Copyfarm. No new pre-clinical or further clinical studies were conducted, which is acceptable for this generic application.

### II. QUALITY ASPECTS

#### II.1 Introduction

Ondansetron Copyfarm is presented in the form of film-coated tablets 4 mg and 8 mg. The drug substance is added as ondansetron hydrochloride dihydrate corresponding to 4 mg and 8 mg ondansetron. The excipients used in the formulation are described in Ph.Eur. and USP/NF. The film-coated tablets are packed in opaque PVC / aluminium foil blisters. The blisters are packed in a cardboard box.

#### II.2 2.2 Drug Substance

Ondansetron hydrochloride dihydrate has a monograph in the Ph.Eur. and the manufacturer holds a Certificate of Suitability of the monograph. It is a white to off white powder. It is sparingly soluble in water. The active substance specification includes relevant tests and the limits for

impurities/degradation products have been justified. The analytical methods applied are sufficiently described and validated.

Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period.

### **II.3 Medicinal Product**

Ondansetron Copyfarm film-coated tablets 4 mg and 8 mg formulated with the excipients anhydrous lactose, microcrystalline cellulose, pregelatinised maize starch, magnesium stearate, hypromellose, titanium dioxide and iron oxide yellow. Lactose is the only material of animal origin used in the manufacture of Ondansetron Copyfarm. A statement from the lactose supplier which confirms that lactose anhydrous has been manufactured from food grade cow's milk sourced from healthy animals in the same condition as milk collected for human consumption has been presented.

The product development has taken the physico-chemical characteristics of the active substance into consideration. The manufacturing process has been sufficiently described and critical steps identified. A process validation plan for the validation studies has been presented. The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies under ICH conditions have been performed and data presented support the shelf life claimed in the SPC. No specific long term storage conditions are required.

## **III. NON-CLINICAL ASPECTS**

Ondansetron Copyfarm has been shown to be essential similar to the approved product Zofran «GlaxoSmithKline». For this abridged application, non-clinical data have not been submitted and are not considered necessary.

## **IV. CLINICAL ASPECTS**

The pharmacodynamics properties and clinical efficacy and safety of ondansetron are well known. As ondansetron is a widely used, well-known active substance, the applicant has not provided additional clinical studies and further studies are not required.

The submitted bioequivalence study shows that Ondansetron Copyfarm 8 mg film-coated tablets are bioequivalent to Zofran «GlaxoSmithKline» 8 mg film-coated tablets with respect to both the rate and extent of absorption of ondansetron, as the values for  $C_{max}$  and AUC were within the acceptance range of 80-125% (90% CI). The study was conducted according to Good Clinical Practice (GCP) and Good Laboratory Practice (GLP) with an adequate design.

The bioequivalence study was performed using the 8 mg tablets, and no bioequivalence studies have been performed with 4 mg tablets. However, the data from the bioequivalence study performed can be extrapolated to the 4mg strength, as the conditions outlined in the CHMP Note for Guidance on the Investigation of Bioavailability and Bioequivalence (NfG) regarding additional strengths, are fulfilled.

The content of the SPC approved during the mutual recognition procedure is in accordance with that for the reference product Zofran, marketed by GlaxoSmithKline.

## **V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION**

Ondansetron Copyfarm film-coated tablets 4 mg and 8 mg is a generic medicinal product to Zofran «GlaxoSmithKline». Zofran is a well-known medicinal product with an established efficacy and safety profile.

The risk/benefit ratio is considered positive and Ondansetron Copyfarm film-coated tablets 4 mg and 8 mg are recommended for approval.

Satisfactory chemical pharmaceutical documentation has been provided assuring consistent quality of the product.

### **List of abbreviations**

ICH	International Conference of Harmonisation
MA	Marketing Authorisation
Ph.Eur.	European Pharmacopoeia
SPC	Summary of Product Characteristics
USP	United States Pharmacopoeia
NF	National Formulary

## **Module 6: Update**