IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PPA1151/077/001
Case No: 2069197

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Imbat Limited

Unit L2, **North Ring Business Park**, **Santry**, **Dublin 9**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Emizof, 4 Milligram

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **26/08/2009**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Emizof 4mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 4mg ondansetron (as ondansetron hydrochloride dihydrate).
Excipients: lactose monohydrate.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.
Product imported from the UK:
Pale yellow, round, biconvex, film-coated tablet embossed with identification marking “41” on one side and plain on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Emizof 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

4.2.1. 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 Emizof should be flexible in the range of 8-32mg a day and selected as shown below.

Emetogenic Chemotherapy and Radiotherapy:
Emizof can be given either by oral or intravenous administration.
For most patients receiving emetogenic chemotherapy or radiotherapy, Emizof 8 mg should be administered as a slow intravenous injection or as a short-time intravenous infusion over 15 minutes immediately before treatment, followed by 8 mg orally twelve hourly.
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 treatment with Emizof 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:
For patients receiving highly emetogenic chemotherapy, e.g. high-dose cisplatin, Emizof can be given by oral or intravenous administration.
(For specific recommendations pertaining to the mode of administration of parenteral forms of ondansetron please refer to the corresponding Summary of Product Characteristics).
To protect against delayed or prolonged emesis after the first 24 hours, oral treatment with Emizof associated with dexamethasone,should be continued for up to 5 days after a course of treatment.

The recommended dose for oral administration is 8mg twice daily.

Use in children (aged 2 years and above) and adolescents (< 18 years)

Experience in paediatric patients is limited. Emizof may be administered as a single intravenous dose of 5mg/m2 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. Children with a total body area between 0.6 and 1.2 m2 should receive a dosage schedule of 4 mg 3 times a day, while children with a body area above 1.2 m2 should receive 8 mg 3 times a day.
There is no experience in children younger than 2 years old.

Use in Elderly patients:
Emizof is well tolerated by patients over 65 years and no alteration of dosage, dosing frequency or route of administration are required.

4.2.2. Post operative nausea and vomiting (PONV)

Prevention of PONV:

Adults: For the prevention of PONV Emizof can be administered orally or by intravenous 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 administration is recommended.

Use in children (aged 2 years and above) and adolescents (< 18 years):

Experience in pediatric patients is limited. For prevention or treatment of established PONV in pediatric patients having surgery performed under general anesthesia, Emizof may be administered with a parenteral form of ondansetron (for specific recommendations pertaining to the mode of administration of parenteral forms of ondansetron please refer to the corresponding Summary of Product Characteristics).

There is limited experience in children under 2 years of age.

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

4.2.3. 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 Emizof 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.

4.3 Contraindications

Hypersensitivity to ondansetron or to other selective 5-HT3 receptor antagonists (e.g. granisetron, dolasetron), or to any of the excipients.

4.4 Special warnings and precautions for use

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

Emizof is not indicated for prevention and treatment of postoperative nausea and vomiting in children after intra-abdominal surgery.

The medicinal product should not be used for children younger than two years, as for these patients the experience is limited.
Since there is little experience to date of the use of Emizof in cardiac patients, caution should be exercised if Emizof is co-administered with anesthetics to patients with arrhythmias or cardiac conduction disorders or to patients who are being treated with antiarrhythmic agents or beta-blockers.Benefit/risk ratio of prescribing Emizof to patients who have previous alteration of the QT interval must be assessed (See 4.8).
In patients with adenotonsillar surgery prevention of nausea and vomiting with Emizof may mask occult bleeding. Therefore, such patients should be followed carefully after Emizof.
This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorpbtion should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

There is no evidence that Emizof either induces or inhibits the metabolism of other drugs commonly co-administered with it. Specific studies have shown that there are no pharmacokinetic interactions when Emizof is administered with alcohol, temazepam, furosemide, tramadol, alfentanil, propofol and thiopental.
Emizof 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 Rifmapicin: 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

Use during pregnancy:
Data on a limited number of exposed pregnancies indicate no undesirable effects of Emizof on pregnancy or on the health of the foetus/newborn infant. 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. However as animal studies are not always predictive of human response the use of Emizof in pregnancy is not recommended.

Use during lactation:
Tests have shown that ondansetron passes into the milk of lactating animals. It is therefore recommended that mothers receiving Emizof should not breast-feed their babies.

4.7 Effects on ability to drive and use machines

Emizof has no influence on the ability to drive and use machines.

4.8 Undesirable effects

Immune system disorders
Rare > 1/10000, < 1/1000): Immediate hypersensitivity reactions, sometimes severe, including anaphylaxis. Anaphylaxis may be fatal.

Hypersensitivity reactions were also observed in patients, who were sensitive towards other selective 5-HT3 antagonists.

Nervous system disorders
Rare > 1/10000, < 1/1000): There have been reports suggestive of involuntary movement disorders such as extrapyramidal reactions e.g. oculogyric crisis/dystonic reactions without definitive evidence of persistent clinical sequelae and seizures have been rarely observed although no known pharmacological mechanism can account for ondansetron causing these effects.

Cardiac disorders
Uncommon (=1/1000 and <1/100): Chest pain, with or without ST segment depression, cardiac arrhythmias, hypotension and bradycardia.
Very rare (< 1/10000 including isolated reports): transient changes in ECG, including lengthening of QT interval, have been reported.
Gastrointestinal disorders
Common > 1/100, < 1/10): ondansetron is known to increase the large bowel transit time and may cause constipation in some patients. Patients with signs of sub acute obstruction should be monitored.

Hepato-biliary disorders
Occasional asymptomatic increases in liver function tests were observed.

Skin and subcutaneous tissue disorders
Occasionally, hypersensitivity reactions around the injection site (e.g. rash, urticaria, itching) may occur, sometimes extending along the medicinal product administration vein.

General disorders and administration site conditions
Common > 1/100, < 1/10): Headache, sensation of flushing or warmth, hiccups.
Rare > 1/10000, < 1/1000): Transient visual disturbances (e.g. blurred vision) and dizziness during rapid intravenous administration of ondansetron.

4.9 Overdose

Little is known at present about overdosage with Emizof, 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 Emizof, therefore in all cases of suspected overdose, symptomatic and supportive therapy should be given as appropriate.
The use of ipecacuanha to treat overdose with Zofran is not recommended as patients are unlikely to respond due to the anti-emetic action of Zofran itself.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

ATC Code: A04A A01

Emizof is a potent, highly selective 5HT3 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 5HT3 receptors. Emizof 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 Emizof in the management of the nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy is probably due to antagonism of 5HT3 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 Emizof has not shown a sedative effect.
Emizof does not alter plasma prolactin concentrations.
The role of Emizof in opiate-induced emesis is not yet established.

5.2 Pharmacokinetic properties

Following oral administration, Emizof is passively and completely absorbed from the gastrointestinal tract and undergoes first pass metabolism (bioavailability is about 60%). Peak plasma concentrations of about 30ng/ml are attained approximately 1.5 hours after an 8mg dose. For doses above 8mg the increase in Emizof 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 Emizof, 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 Emizof 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 Emizof.
A 4mg intravenous infusion of Emizof given over 5 minutes results in peak plasma concentrations of about 65ng/ml. Following intramuscular administration of Emizof, peak plasma concentrations of about 25ng/ml are attained within 10 minutes of injection.
Emizof is not highly protein bound (70-76%). Emizof 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 Emizof 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 Emizof, 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. Studies in healthy elderly volunteers have shown slight age-related increases in both oral bioavailability (65%) and half-life (5 hours).
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.

Emizof and its metabolites accumulate in the milk of rats, milk/plasma-ratio was 5.2.
Emizof in submicromolar concentrations blocked cloned HERG Potassium channels of the human heart. The clinical relevance of this finding is not clear.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

lactose monohydrate
microcrystalline cellulose (E460)
Starch, pregelatinised maize
magnesium stearate (E572)
hypromellose (E464)
titanium dioxide (E171)
propylene glycol (E1520)
sorbitan monooleate (E494)
sorbic acid (E200)
vanillin
quinoline yellow (E104)
hydroxypropyl cellulose (E463).

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

The shelf life expiry date of this product shall be the date shown on the container and outer package of the product on the market in the country of origin.

6.4 Special precautions for storage

Do not store above 30°C

6.5 Nature and contents of container

Re-boxed carton containing blister strips. Pack size 30.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements

7 Parallel Product Authorisation Holder

Imbat Limited
Unit L2
North Ring Business Park
Santry
Dublin 9

8 Parallel Product Authorisation Number

PPA 1151/77/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation : 29th August 2008

10 DATE OF REVISION OF THE TEXT

August 2009