SUMMARY OF PRODUCT CHARACTERISTICS

NAME OF THE MEDICINAL PRODUCT

Cruzafen® injection 8mg/4mL
Cruzafen® tablets 8mg
Cruzafen® oral solution 8mg/10mL

ALITATIVE AND QUANTITATIVE COMPOSITION: Each **Cruzafen® tablet 8mg** is a te film coated tablet containing ondansetron 8mg (as hydrochlotide dihydrate). Each **Cruzafen® ction 8mg/4mL** is a 4mL glass ampoule containing 8mg ondansetron (as hydrochloride drate) in aqueous solution for intravenous or intramuscular administration. Each **Cruzafen® l solution 8mg/10mL** is a 50mL aqueous sugar free solution in a glass bottle. Each 10mL tains 8mg ondansetron (as hydrochloride dihydrate).

INICAL PARTICULARS

rapeutic indications: 1. Management of nausea and vomiting induced by cytotoxic notherapy and radiotherapy **2.** Prevention and treatment of post-operative nausea and vomiting.

ology and method of administration

motherapy and radiotherapy induced nausea and vomiting

dts: The emetogenic potential of cancer treatment varies according to the doses and ibinations of chemotherapy and radiotherapy regimens used. The route of administration and s of Cruzafen® should be flexible in the range of 8-32mg a day and selected as shown below.

derately emetogenic chemotherapy and radiotherapy: Cruzafen® can be given either by oral lets or oral solution), intravenous or intramuscular administration. For oral administration: 8mg hours before treatment, followed by 8mg 12 hours later. For parenteral administration: 8mg as a e intravenous or intramuscular injection immediately before treatment, followed by 8mg orally ive hourly. To protect against delayed or prolonged emesis after the first 24 hours, oral tment with Cruzafen® should be continued for up to 5 days after a course of treatment. The mmended dose is 8mg twice daily.

hly emetogenic chemotherapy: For patients receiving highly emetogenic chemotherapy, eg. h-dose cisplatin, Cruzafen® can be given either by oral or by intravenous or intramuscular inistration. The recommended dose for oral administration is 24mg given one or two hours e to chemotherapy.

recommended dose for i.v./i.m. administration is 8mg by slow intravenous or intramuscular ction immediately before chemotherapy, followed by two further intravenous or intramuscular es of 8mg two to four hours apart, or by a constant infusion of 1mg/hour for up to 24 hours. rnatively, the recommended i.v./i.m. dose is a single 32mg dose diluted in 50-100mL of saline ther compatible infusion fluid and infused over not less than 15 minutes immediately before notherapy.

selection of dose regimen should be determined by the severity of the emetogenic challenge. protect against delayed or prolonged emesis after the first 24 hours, oral treatment with zafen® should be continued for up to 5 days after a course of treatment.

ldren: Cruzafen® may be administered as a single intravenous dose of 5mg/m^2 immediately ore chemotherapy, followed by 4mg orally twelve hours later. 4mg orally twice daily should be inued for up to 5 days after a course of treatment.

erly: Cruzafen® is well tolerated by patients over 65 years and no alteration of dosage, dosing uency or route of administration are required.

the prevention of PONV: Cruzafen® can be administered orally or by intravenous or muscular injection.

oral administration: 16mg one hour prior to anaesthesia. Alternatively, 8mg one hour prior to
esthesia followed by two further doses of 8mg at eight hourly intervals.
i.v./i.m. administration: 4mg given by intramuscular or slow intravenous injection at induction
naesthesia.
treatment of established PONV a single dose of 4mg given by intramuscular or slow
ivenous injection is recommended.

ldren (aged 2 years and over): For prevention of PONV in paediatric patients having surgery
ormed under general anaesthesia, ondansetron may be administered by slow intravenous
ction at a dose of 0.1mg/kg up to a maximum of 4mg, either prior to, at or after induction of
esthesia.
re is limited data on the use of Cruzafen® in the prevention and treatment of PONV in children
er 2 years of age.

erly: There is limited experience in the use of Cruzafen® in the prevention and treatment of
-operative nausea and vomiting in the elderly, however Cruzafen® is well tolerated in patients
r 65 years receiving chemotherapy.

ients with renal impairment: No alteration of daily dosage or frequency of dosing, or route of
inistration are required.

ients with hepatic impairment: Clearance of Cruzafen® is significantly reduced and serum
-life significantly prolonged in subjects with moderate or severe impairment of hepatic function.
uch patients a total daily dose of 8mg should not be exceeded.

ients with poor sparteine/debrisoquine metabolism: The elimination half-life of ondansetron
ot altered in subjects classified as poor metabolisers of sparteine and debrisoquine.
sequently in such patients repeat dosing will give drug exposure levels no different from those
se general population. No alteration of daily dosage or frequency of dosing are required.

traindications Hypersensitivity to any component of the preparation.

cial warnings and precautions for use Hypersensitivity reactions have been reported in
ents who have exhibited hypersensitivity to other selective $5HT_3$ receptor antagonists.
ondansetron is known to increase large bowel transit time, patients with signs of subacute
stinal obstruction should be monitored following administration.

raction with other medicinal products and other forms of interaction There is no evidence
ondansetron either induces or inhibits the metabolism of other drugs commonly coadministered
ı it. Specific studies have shown that ondansetron does not interact with alcohol, temazepam,
emide, tramadol and propofol.

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

cts on ability to drive and use machines In psychomotor testing ondansetron does not impair
ormance nor cause sedation.

lesirable effects Ondansetron is known to increase large bowel transit time and may cause
stipation in some patients. The following side effects can occur: headache, a sensation of
hing or warmth, hiccups and occasional asymptomatic increases in liver function tests. There
e been rare reports of immediate hypersensitivity reactions sometimes severe including
aphylaxis. Rare cases of transient visual disturbances (e.g., blurred vision) and dizziness have
ı reported during rapid intravenous administration of ondansetron. There have been rare reports
gestive of extrapyramidal reactions such as oculogyric crisis/dystonic reactions without
nitive evidence of persistent clinical sequelae, and seizures have been rarely observed although

known pharmacological mechanism can account for ondansetron causing these effects. Chest
with or without ST segment depression, cardiac arrhythmias, hypotension and bradycardia
been rarely reported.

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

ARMACOLOGY

rmacodynamic properties: Ondansetron is a potent, highly selective 5-HT_3 receptor-
gonist. Its precise mode of action in the control of nausea and vomiting is not known.
motherapeutic agents and radiotherapy may cause release of 5HT in the small intestine
ating a vomiting reflex by activating vagal afferents via $5HT_3$ receptors. Ondansetron blocks the
ation of this reflex. Activation of vagal afferents may also cause a release of 5HT in the area
rema, located on the floor of the fourth ventricle, and this may also promote emesis through a
ral mechanism. Thus, the effect of ondansetron in the management of the nausea and vomiting
ced by cytotoxic chemotherapy and radiotherapy is probably due to antagonism of $5HT_3$
ptors on neurons located both in the peripheral and central nervous system. The mechanisms of
on in post-operative nausea and vomiting are not known but there may be common pathways
cytotoxic induced nausea and vomiting. The role of ondansetron in opiate-induced emesis is
yet established. Ondansetron does not alter plasma prolactin concentrations.

rmacokinetic properties Following oral administration, ondansetron is passively and
pletely absorbed from the gastrointestinal tract and undergoes first pass metabolism. Peak
ma concentrations of about 26,2ng/mL for men and 47,7ng/mL for women are attained after 2
1,7 hours respectively after an 8mg dose. Absolute bioavailability is about 56%. Following oral
inistration of 24mg ondansetron, peak plasma concentrations of about 125,80ng/mL for men
194,40ng/mL for women are attained after 1,9 and 1,6 hours respectively.
ze 8-mg tablets are bioequivalent and interchangeable to one 24-mg tablet.
doses above 8mg the increase in ondansetron systemic exposure with dose is greater than
portional; this may reflect some reduction in first pass metabolism at higher oral doses.
vailability, following oral administration, is slightly enhanced by the presence of food but
ffected by antacids. Studies in healthy elderly volunteers have shown slight, but clinically
gnificant, age-related increases in both oral bioavailability (65%) and half-life (5 hours) of
ansetron. Gender differences were shown in the disposition of ondansetron, with females having
aster rate and extent of absorption following an oral dose and reduced systemic clearance and
me of distribution (adjusted for weight). The disposition of ondansetron following oral,
muscular and intravenous dosing is similar with a terminal half life of about 3 hours and steady
volume of distribution of about 140L. Equivalent systemic exposure is achieved after IM and
dministration of ondansetron. A 4mg intravenous infusion of ondansetron given over 5 minutes
lts in peak plasma concentrations of about 65ng/mL. Following intramuscular administration of
ansetron, peak plasma concentrations of about 25ng/mL are attained within 10 minutes of
ction. Ondansetron is not highly protein bound (70-76%). Ondansetron is cleared from the
emic circulation predominantly by hepatic metabolism through multiple enzymatic pathways.
than 5% of the absorbed dose is excreted unchanged in the urine. The absence of the enzyme
P2D6 (the debrisoquine polymorphism) has no effect on ondansetron's pharmacokinetics. The
rmacokinetic properties of ondansetron are unchanged on repeat dosing. In a study of 21
diatric patients aged between 3 and 12 years undergoing elective surgery with general
esthesia, the absolute values for both the clearance and volume of distribution of ondansetron
owing a single intravenous dose of 2mg (3-7 years old) or 4mg (8-12 years old) were reduced.

magnitude of the change was age-related, with clearance falling from about 300mL/min at 12
rs of age to 100mL/min at 3 years. Volume of distribution fell from about 75L at 12 years to
at 3 years. Use of weight-based dosing (0.1mg/kg up to 4mg maximum) compensates for these
ages and is effective in normalising systemic exposure in paediatric patients. In patients with
d impairment (creatinine clearance 15-60mL/min), both systemic clearance and volume of
ribution are reduced following IV administration of ondansetron, resulting in a slight, but
ically insignificant, increase in elimination half-life (5.4h). A study in patients with severe renal
airment who required regular haemodialysis (studied between dialyses) showed ondansetron's
rmacokinetics to be essentially unchanged following IV administration. Specific studies in the
rly or patients with renal impairment have been limited to IV and oral administration. However,
anticipated that the half-life of ondansetron after rectal administration in these populations will
imilar to that seen in healthy volunteers, since the rate of elimination of ondansetron following
al administration is not determined by systemic clearance.

owing oral, intravenous or intramuscular dosing in patients with severe hepatic impairment,
nsetron's systemic clearance is markedly reduced with prolonged elimination half-lives (15-32
nd an oral bioavailability approaching 100% due to reduced pre-systemic metabolism.

clinical safety data No additional data of relevance.

ARMACEUTICAL PARTICULARS

xtion solution: Citric acid monohydrate, sodium citrate, sodium chloride, water for injection.

dets: Lactose, microcrystalline cellulose, pregelatinised maize starch, magnesium stearate,
hylhydroxypropylcellulose, titanium dioxide (E171), iron oxide yellow. **Oral solution:** citric
, sodium citrate dihydrate, sodium benzoate, sorbitol solution, strawberry flavour, purified
er.

mpatibilities None reported for Cruzafen® tablets or oral solution. Cruzafen® injection should
be administered in the same syringe or infusion as any other medication.

lf-life

xtion solution: 36 months (unopened). 24 hours (dilutions stored 2-8°C). **Tablets:** 36 months.

l solution: 36 months.

cial precautions for storage

xtion solution: Protect from light. Store below 30°C. Dilutions of Cruzafen® injection in
patible intravenous infusion fluids are stable under normal room lighting conditions or daylight
t least 24 hours, thus no protection from light is necessary while infusion takes place. **Tablets:**
e below 30°C. **Oral solution:** Store below 30°C. Do not refrigerate.

ure and contents of container

zafen® injection: Type I clear glass snap-ring ampoules in a carton box. **Cruzafen® tablets:**
/PVDC-aluminum foil blister of 15 tablets in a carton box. **Oral solution:** Carton box
aining type III 60mL amber glass bottle with a white cap. Bottle contains 50mL of oral
sion.

ructions for use and handling

patibility with intravenous fluids: Cruzafen® injection should only be admixed with those
sion solutions which are recommended: Sodium Chloride Intravenous Infusion 0.9%w/v,
cose Intravenous Infusion 5%w/v, Mannitol Intravenous Infusion 10%w/v, Ringers Intravenous
sion,

ssium Chloride 0.3%w/v and Sodium Chloride 0.9%w/v Intravenous Infusion, Potassium
oride 0.3%w/v and Glucose 5%w/v Intravenous Infusion.

eeping with good pharmaceutical practice dilutions of Cruzafen® injection in intravenous fluids
ld be prepared at the time of infusion or stored at 2-8°C for no more than 24 hours before the
of administration. Compatibility studies have been undertaken in polyvinyl chloride infusion
s and polyvinyl chloride administration sets. It is considered that adequate stability would also
conferred by the use of polyethylene infusion bags or Type 1 glass bottles. Dilutions of

zafen" in sodium chloride 0.9%w/v or in glucose 5%w/v have been demonstrated to be stable in
propylene syringes. It is considered that Cruzafen® injection diluted with other compatible
sion fluids would be stable in polypropylene syringes. **Compatibility with other drugs:**
zafen® may be administered by intravenous infusion at 1mg/hour, e.g. from an infusion bag or
nge pump. The following drugs may be administered via the Y-site of the Cruzafen® giving set
ondansetron concentrations of 16 to 160 micrograms/mL (e.g. 8mg/500mL and 8mg/50mL
ectively); **Cisplatin:** Concentrations up to 0.48mg/mL (e.g. 240mg in 500mL) administered
r one to eight hours. **5 -Fluorouracil:**
centrations up to 0.8mg/mL (e.g. 2.4g in 3 litres or 400mg in 500mL) administered at a rate of
ast 20mL per hour (500mL per 24 hours). Higher concentrations of 5-fluorouracil may cause
ipitation of ondansetron. The 5-fluorouracil infusion may contain up to 0.045%w/v $MgCl_2$ in
tion to other excipients shown to be compatible. **Carboplatin:** Concentrations in the range
1mg/mL to 9.9mg/mL (e.g. 90mg in 500mL to 990mg in 100mL), administered over ten minutes
ne hour. **Etoposide:** Concentrations in the range 0.14mg/mL to 0.25mg/mL (e.g. 72mg in
mL to 250mg in 1 litre), administered over thirty minutes to one hour. **Ceftazidime:** Doses in
range 250mg to 2000mg reconstituted with Water for Injections as recommended by the
nufacturer (e.g. 2.5mL for 250mg and 10mL for 2g ceftazidime) and given as an intravenous
s injection over approximately five minutes. **Cyclophosphamide:** Doses in the range 100mg to
reconstituted with Water for Injections, 5mL per 100mg cyclophosphamide, as recommended
he manufacturer and given as an intravenous bolus injection over approximately five minutes.
orubicin: Doses in the range 10-100mg reconstituted with Water for Injections, 5mL per 10mg
orubicin, as recommended by the manufacturer and given as an intravenous bolus injection over
roximately 5 minutes. **Dexamethasone:** Dexamethasone sodium phosphate 20mg may be
inistered as a slow intravenous injection over 2-5 minutes via the Y-site of an infusion set
verting 8 or 32mg of ondansetron diluted in 50-100mL of a compatible infusion fluid over
roximately 15 minutes. Compatibility between dexamethasone sodium phosphate and
ansetron has been demonstrated supporting administration of these drugs through the same
ng set resulting in concentrations in line of 32 microgram - 2.5mg/mL for dexamethasone
ium phosphate and 8 microgram-1mg/mL for ondansetron.

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RKETING AUTHORISATION NUMBERS Cruzafen® injection solution 8mg/4mL:
47/03/30-4-2004, Cruzafen® tabs 8mg: 62333/03/30-4-2004, Cruzafen® oral solution
g/10mL: 62350/03/17-3-2004.

TE OF FIRST AUTHORISATION Cruzafen® tablets 8mg: 18375/20-5-2002, Cruzafen® in-
ion 8mg/4mL: 18376/20-5-2002.