1. TRADE NAME OF THE MEDICINAL PRODUCT

Zofran® Tablets 4 mg
Zofran® Tablets 8 mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Zofran Tablet 4mg contains ondansetron 4 mg (as hydrochloride dihydrate).
Each Zofran Tablet 8mg contains ondansetron 8 mg (as hydrochloride dihydrate).

Excipients with known effect:
Zofran Tablets 4 mg: contains lactose (anhydrous) 81.875 mg (see section 4.4).
Zofran Tablets 8 mg: contains lactose (anhydrous) 163.75 mg (see section 4.4).

For the full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Film coated tablet.
Zofran Tablet 4mg is a yellow, oval, biconvex tablet engraved with "GXET3" on one face and plain on the other.
Zofran Tablet 8mg is a yellow, oval, biconvex tablet engraved with "GXET5" on one face and plain on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Adults:
Zofran is indicated for the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy.
Zofran is indicated for the prevention and treatment of post-operative nausea and vomiting (PONV).

Paediatric Population:
Zofran is indicated for the management of nausea and vomiting induced by cytotoxic chemotherapy.

4.2 Posology and Method of Administration

Posology
Chemotherapy and radiotherapy induced nausea and vomiting (CINV and RINV).

Adults

The emetogenic potential of cancer treatment varies according to the doses and combinations of chemotherapy and radiotherapy regimens used. The selection of dose regimen should be determined by the severity of the emetogenic challenge.

Emetogenic Chemotherapy and Radiotherapy: Zofran can be given either by oral (tablets), intravenous or intramuscular administration.

The recomended oral dose is: 8 mg taken 1 to 2 hours before chemotherapy or radiation treatment, followed by 8mg every 12 hours for a maximum of 5 days to protect against delayed or prolonged emesis.

For highly emetogenic chemotherapy To protect against delayed or prolonged emesis after the first 24 hours, oral treatment with Zofran may be continued for up to 5 days after a course of treatment.

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

Paediatric Population

Ondansetron may be administered as a single intravenous dose of 5 mg/m^2 immediately before chemotherapy, followed by 4 mg orally twelve hours later. 4 mg orally twice daily can be continued for up to 5 days after a course of treatment.

Elderly

Zofran is well tolerated by patients over 65 years. No alteration of oral dose or frequency of administration is required.

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 Zofran 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 is required.

Post operative nausea and vomiting (PONV):

Adults

For the prevention of PONV: ondansetron can be administered orally or by intravenous or intramuscular injection.
The recommended oral dose is 16mg taken one hour prior to anaesthesia.

For the treatment of established PONV, intravenous or intramuscular administration is recommended.
Children and Adolescents aged 2 years and over

No studies have been conducted on the use of orally administered ondansetron in the prevention or treatment of post operative nausea and vomiting; slow i.v. injection is recommended for this purpose.

Elderly

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

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 Zofran 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 is required.

Method of Administration
The tablets should be swallowed whole with liquid.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Concomitant use with apomorphine is contraindicated (see section 4.5 interactions)

4.4 Special warnings and precautions for use

Hypersensitivity reactions have been reported in patients who have exhibited hypersensitivity to other selective $5HT_3$ receptor antagonists. Respiratory events should be treated symptomatically and clinicians should pay particular attention to them as precursors of hypersensitivity reactions.

Ondansetron prolongs the QT interval in a dose-dependent manner (see section 5.1). In addition, post-marketing cases of Torsade de Pointes have been reported in patients using ondansetron. Avoid ondansetron in patients with congenital long QT syndrome. Ondansetron should be administered with caution to patients who have or may develop prolongation of QTc, including patients with electrolyte abnormalities, congestive heart failure, bradyarrhythmias or patients taking other medicinal products that lead to QT prolongation or electrolyte abnormalities.

Myocardial ischemia has been reported in patients treated with ondansetron. In some cases, predominantly during intravenous administration, the symptoms appeared immediately after administration but recovered with prompt treatment. Therefore, caution should be exercised during and after administration of ondansetron.

Hypokalaemia and hypomagnesaemia should be corrected prior to ondansetron administration.

The development of serotonin syndrome has been reported with 5-HT3 receptor antagonists alone. Most reports have been associated with concomitant use of serotonergic drugs (e.g., selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase inhibitors, mirtazapine, fentanyl, lithium, tramadol, and intravenous methylene blue). Some of the reported cases were fatal. Serotonin syndrome occurring with overdose of Zofran alone has also been reported. The majority of reports of serotonin syndrome related to $5\text{-}HT_3$ receptor antagonist use occurred in a post-anesthesia care unit or an infusion center. Symptoms associated with serotonin syndrome may include the following combination of signs and symptoms: mental status changes (e.g., agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular symptoms (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, with or without gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Patients should be monitored for the emergence of serotonin syndrome, especially with concomitant use of Zofran and other serotonergic drugs. If symptoms of serotonin syndrome occur, discontinue Zofran and initiate supportive treatment. Patients should be informed of the increased risk of serotonin syndrome, especially if Zofran is used concomitantly with other serotonergic drugs (see sections 4.5 and 4.9).

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.

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

Paediatric Population:

Paediatric patients receiving ondansetron with hepatotoxic chemotherapeutic agents should be monitored closely for impaired hepatic function.

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 coadministered with it. Specific studies have shown that there are no interactions when ondansetron is administered with alcohol, temazepam, furosemide, alfentanil, tramadol, morphine, lidocaine, thiopental, or 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.

Caution should be exercised when ondansetron is coadministered with drugs that prolong the QT interval and/or cause electrolyte abnormalities (see section 4.4).

Use of ondansetron with QT prolonging drugs may result in additional QT prolongation. Concomitant use of ondansetron with cardiotoxic drugs (e.g. anthracyclines (such as doxorubicin, daunorubicin) or trastuzumab), antibiotics (such as erythromycin), antifungals (such as ketoconazole, antiarrhythmics (such as amiodarone) and beta blockers (such as atenolol or timolol) may increase the risk of arrhythmias. (see section 4.4).

Serotonergic Drugs: Serotonin syndrome (including altered mental status, autonomic instability, and neuromuscular symptoms) has been described following the concomitant use of 5-HT_3 receptor antagonists and other serotonergic drugs, including SSRIs and SNRIs (see section 4.4).
Monitor for the emergence of serotonin syndrome. If symptoms occur, discontinue ZOFRAN and initiate supportive treatment *[see Special warnings and precautions for use (4.4)].*

Apomorphine: Based on reports of profound hypotension and loss of consciousness when ondansetron was administered with apomorphine hydrochloride, concomitant use with apomorphine is contraindicated.

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 Fertility, pregnancy and lactation

Pregnancy

Based on human experience of epidemiological studies, ondansetron is suspected to cause orofacial malformations when administered during first trimester of pregnancy.

In one cohort study including 1.8 million pregnancies, first trimester ondansetron use was associated with an increased risk of oral clefts (3 additional cases per 10,000 women treated; adjusted relative risk, 1.24 (95% CI 1.03 to 1.48).

The available epidemiological studies on cardiac malformations show conflicting results. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity.

The use of ondansetron in pregnancy is not recommended.

Breast-feeding

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

Fertility

There is no information on the effects of ondansetron on human fertility.

4.7 Effects on ability to drive and use machines

Zofran has no or negligible influence on the ability to drive and use machines. In psychomotor testing ondansetron does not impair performance nor cause sedation. No detrimental effects on such activities are predicted from the pharmacology of ondansetron**.**

4.8 Undesirable effects

Tabulated list of adverse reactions

Adverse events are listed below by system organ class and frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000) and not known (cannot be estimated from the available data). Very common, common and uncommon events were generally determined from clinical trial data. The incidence in placebo was taken into account. Rare, very rare and not known events were generally determined from post-marketing spontaneous data.

The following frequencies are estimated at the standard recommended doses of ondansetron. The adverse event profiles in children and adolescents were comparable to that seen in adults.

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)[(1)].
Rare:	Dizziness predominantly during rapid IV administration.
Eye disorders	
Rare:	Transient visual disturbances (e.g. blurred vision) predominantly during IV administration.
Very rare:	Transient blindness predominantly during IV administration [(2)].
Cardiac disorders	
Uncommon:	Arrhythmias, chest pain with or without ST segment depression, bradycardia.
Rare:	QTc prolongation (including Torsade de Pointes).
Not known	Myocardial ischemia*
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 [(3)].

1. Observed without definitive evidence of persistent clinical sequelae.
2. 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.
3. These events were observed commonly in patients receiving chemotherapy with cisplatin.

* These types of adverse drug reactions have been derived from post-marketing experience with Zofran via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il

4.9 Overdose

Symptoms and Signs

There is limited experience of ondansetron overdose. In the majority of cases, symptoms were similar to those already reported in patients receiving recommended doses (see section 4.8). Manifestations that have been reported include visual disturbances, severe constipation, hypotension and a vasovagal episode with transient second-degree AV block.

Ondansetron prolongs the QT interval in a dose-dependent fashion. ECG monitoring is recommended in cases of overdose.

Paediatric population

Paediatric cases consistent with serotonin syndrome have been reported after inadvertent oral overdoses of ondansetron (exceeding estimated ingestion of 5 mg/kg) in young children. Reported symptoms included somnolence, agitation, tachycardia, tachypnea, hypertension, flushing, mydriasis, diaphoresis, myoclonic movements, horizontal nystagmus, hyperreflexia, and seizure. Patients required supportive care, including intubation in some cases, with complete recovery without sequelae within 1 to 2 days.

Management

There is no specific antidote for ondansetron, therefore in all cases of suspected overdose, symptomatic and supportive therapy should be given as appropriate.

Further management should be as clinically indicated or as recommended by the national poisons centre, where available.

The use of ipecacuanha to treat overdose with ondansetron is not recommended, as patients are unlikely to respond due to the anti-emetic action of ondansetron itself.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Serotonin (5HT3) antagonist, ATC code: A04AA01

Mechanism of action

Ondansetron 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. 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 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.

Ondansetron does not alter plasma prolactin concentrations.

Clinical safety and efficacy

The role of ondansetron in opiate-induced emesis is not yet established.

QT Prolongation

The effect of ondansetron on the QTc interval was evaluated in a double blind, randomized, placebo and positive (moxifloxacin) controlled, crossover study in 58 healthy adult men and women. Ondansetron doses included 8 mg and 32 mg infused intravenously over 15 minutes. At the highest tested dose of 32 mg, the maximum mean (upper limit of 90% CI) difference in QTcF from placebo after baseline-correction was 19.6 (21.5) msec. At the lower tested dose of 8 mg, the maximum mean (upper limit of 90% CI) difference in QTcF from placebo after baseline-correction was 5.8 (7.8) msec. In this study, there were no QTcF measurements greater than 480 msec and no QTcF prolongation was greater than 60 msec.

Paediatric population

CINV

The efficacy of ondansetron in the control of emesis and nausea induced by cancer chemotherapy was assessed in a double-blind randomised trial in 415 patients aged 1 to 18 years (S3AB3006). On the days of chemotherapy, patients received either ondansetron 5 mg/m^2 intravenous and ondansetron 4 mg orally after 8 to 12 hours or ondansetron 0.45 mg/kg intravenous and placebo orally after 8 to 12 hours. Post-chemotherapy both groups received 4 mg ondansetron syrup twice daily for 3 days. Complete control of emesis on worst day of chemotherapy was 49% (5 mg/m^2 intravenous and ondansetron

4 mg orally) and 41% (0.45 mg/kg intravenous and placebo orally). Post-chemotherapy both groups received 4 mg ondansetron syrup twice daily for 3 days. There was no difference in the overall incidence or nature of adverse events between the two treatment groups.

A double-blind randomised placebo-controlled trial (S3AB4003) in 438 patients aged 1 to 17 years demonstrated complete control of emesis on worst day of chemotherapy in:

- 73% of patients when ondansetron was administered intravenously at a dose of 5 mg/m^2 intravenous together with 2 to 4 mg dexamethasone orally
- 71% of patients when ondansetron was administered as syrup at a dose of 8 mg together with 2 to 4 mg dexamethasone orally on the days of chemotherapy.

Post-chemotherapy both groups received 4 mg ondansetron syrup twice daily for 2 days. There was no difference in the overall incidence or nature of adverse events between the two treatment groups.

The efficacy of ondansetron in 75 children aged 6 to 48 months was investigated in an open-label, non-comparative, single-arm study (S3A40320). All children received three 0.15 mg/kg doses of intravenous ondansetron, administered 30 minutes before the start of chemotherapy and then at 4 and 8 hours after the first dose. Complete control of emesis was achieved in 56% of patients.

Another open-label, non-comparative, single-arm study (S3A239) investigated the efficacy of one intravenous dose of 0.15 mg/kg ondansetron followed by two oral ondansetron doses of 4 mg for children aged < 12 years and 8 mg for children aged ≥ 12 years (total no. of children n= 28). Complete control of emesis was achieved in 42% of patients.

5.2 Pharmacokinetic properties

Absorption

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. Mean bioavailability in healthy male subjects, following the oral administration of a single 8 mg tablet, is approximately 55 to 60%. Bioavailability, following oral administration, is slightly enhanced by the presence of food but unaffected by antacids.

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 4 mg 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.

Distribution
Ondansetron is not highly protein bound (70-76%).

Biotransformation and Elimination
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.

Special Patient Populations:

Gender

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).
Children and Adolescents (aged 1 month to 17 years)

Population pharmacokinetic analysis was performed on 428 subjects (cancer patients, surgery patients and healthy volunteers) aged 1 month to 44 years following intravenous administration of ondansetron. Based on this analysis, systemic exposure (AUC) of ondansetron following oral or IV dosing in children and adolescents was comparable to adults, with the exception of infants aged 1 to 4 months. Volume was related to age and was lower in adults than in infants and children. Clearance was related to weight but not to age with the exception of infants aged 1 to 4 months. It is difficult to conclude whether there was an additional reduction in clearance related to age in infants 1 to 4 months or simply inherent variability due to the low number of subjects studied in this age

group. Since patients less than 6 months of age will only receive a single dose in PONV a decreased clearance is not likely to be clinically relevant.

Elderly
Early Phase I studies in healthy elderly volunteers showed a slight age-related decrease in clearance, and an increase in half-life of ondansetron. However, wide inter-subject variability resulted in considerable overlap in pharmacokinetic parameters between young (< 65 years of age) and elderly subjects (≥ 65 years of age) and there were no overall differences in safety or efficacy observed between young and elderly cancer patients enrolled in CINV clinical trials to support a different dosing recommendation for the elderly.

Based on more recent ondansetron plasma concentrations and exposure-response modelling, a greater effect on QTcF is predicted in patients ≥75 years of age compared to young adults. Specific dosing information is provided for patients over 65 years of age and over 75 years of age for intravenous dosing.

Renal impairment
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 (5.4 hours). 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.

Hepatic impairment
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 hours) 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

Embryo-fetal development studies in rats and rabbits did not show evidence of harm to the fetus when ondansetron was administered during the period of organogenesisat at approximately 6 and 24 times respectively the maximum recommended human oral dose of 24 mg/day, based on body surface area. In a pre- and postnatal developmental toxicity study, there were no effects upon pregnant rats and the pre- and postnatal development of their offspring, including reproductive performance at approximately 6 times the maximum recommended human oral dose of 24 mg/day based on body surface area.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose (anhydrous), microcrystalline cellulose, pregelatinised maize starch, methylhydroxypropyl cellulose, magnesium stearate, titanium dioxide (E171), iron oxide yellow (E172).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Store below 30ºC.

6.5 Nature and contents of container

Blister packs of 10 tablets comprising aluminium/PVC blister film and aluminium foil lidding.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Registration holder and Importer and its address

Novartis Israel Ltd., POB 7126, Tel-Aviv

8. Registration number

Zofran Tablets 4 mg 049-96-26549
Zofran Tablets 8 mg 049-95-26560

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