2056457

Promesec Capsule 20mg

Each capsule contains 20 mg of Omeprazole

THERAPEUTIC INDICATIONS

Promesec Capsule 20mg are indicated for treatment of:

- Duodenal ulcer
- Gastric ulcer
- NSAID associated gastric and duodenal ulcers or erosions
- Helicobacter pylori eradication in peptic ulcer disease
- Reflux oesophagitis
- Symptomatic gastro-oesophageal reflux disease
- Zollinger-Ellison syndrome
- Acid related dyspepsia

POSOLOGY

Duodenal ulcer

The recommended dosage in patients with an active duodenal ulcer is omeprazole 20 mg once daily. Symptom resolution is rapid and in most patients healing occurs within 2 weeks. For those patients who may not be fully healed after the initial course, healing usually occurs during a further 2 week treatment period.

In patients with poorly responsive duodenal ulcer omeprazole 40mg once daily is recommended and healing is usually achieved within 4weeks.

For the prevention of relapse in patients with duodenal ulcer disease the recommended dose is omeprazole 10 mg once daily. If needed the dose can be increased to omeprazole 20¬40mg once daily.

For NSAID associated duodenal ulcers see NSAID associated gastroduodenal lesions.

For eradication of Helicobacter pylori see Helicobacter pylori (Hp) eradication regimens in peptic ulcer disease.

Gastric ulcer

The recommended dosage is omeprazole 20 mg once daily. Symptom resolution is rapid and in most patients healing occurs within 4 weeks. For those patients who may not be fully healed after the initial course, healing usually occurs during a further 4 weeks treatment period.

In patients with poorly responsive gastric ulcer omeprazole 40 mg once daily is recommended and healing is usually achieved within 8 weeks.

For the prevention of relapse in patients with poorly responsive gastric ulcer the recommended dose is omeprazole 20 mg once daily. If needed the dose can be increased to omeprazole 40 mg once daily.

For eradication of Helicobacter pylori see Helicobacter pylori (Hp) eradication regimens in peptic ulcer disease.

NSAID associated ulcers or gastroduodenal erosions

NSAID associated gastric ulcers, duodenal ulcers or gastroduodenal erosions in patients without continued NSAID treatment the recommended dosage of omeprazole is 20 mg once daily. Symptom resolution is rapid and in most patients healing occurs within 4 weeks. For those patients who may not be fully healed after the initial course, healing usually occurs during a further 4 weeks treatment period.

For the prevention of NSAID associated gastric ulcers, duodenal ulcers, gastroduodenal erosions and dyspeptic symptoms the recommended dosage of omeprazole is 20 mg once daily.

Helicobacter pylori (Hp) eradication regimens in peptic ulcer disease

Triple therapy regimens:

Omeprazole 20 mg, amoxicillin 1 g and clarithromycin 500 mg, all twice a day for one week or

Omeprazole 20 mg, metronidazole 400 mg (or tinidazole 500 mg) and clarithromycin 250mg, all twice a day for one week, or

Omeprazole 40 mg once daily with amoxicillin 500 mg and metronidazole 400 mg both three times a day for one week.

Dual therapy regimens:

Omeprazole 40¬80 mg daily with amoxicillin 1.5 g daily in divided doses for two weeks. In clinical studies daily doses of 1.5¬3 g of amoxicillin have been used, or

Omeprazole 40mg once daily and clarithromycin 500 mg three times a day for two weeks.

To ensure healing in patients with active peptic ulcer disease, see further dosage recommendations for Duodenal and Gastric ulcer.

In each regimen if the patient is still Hp positive, therapy may be repeated.

Reflux oesophagitis

The recommended dosage is omeprazole 20 mg once daily. Symptom resolution is rapid and in most patients healing occurs within 4 weeks. For those patients who may not be fully healed after the initial course, healing usually occurs during a further 4 weeks treatment period.

In patients with severe reflux oesophagitis omeprazole 40 mg once daily is recommended and healing is usually achieved within 8 weeks.

For the long term management of patients with healed reflux oesophagitis the recommended dose is omeprazole 10 mg once daily. If needed the dose can be increased to omeprazole 20¬40mg once daily.

Symptomatic gastro-oesophageal reflux disease

The recommended dosage is omeprazole 20 mg daily. Symptom relief is rapid. Patients may respond adequately to 10 mg daily, and therefore individual dose adjustment should be considered. If symptom control has not been achieved after 4 weeks treatment with omeprazole 20mg daily, further investigation is recommended

Acid related dyspepsia

In the relief of symptoms in patients with epigastric pain/discomfort with or without heartburn the recommended dosage is omeprazole 20 mg once daily.

Patients may respond adequately to 10 mg daily and therefore this dose could be considered as a starting dose.

If symptom control has not been achieved after 4 weeks treatment with omeprazole 20mg daily, further investigation is recommended.

Zollinger Ellison Syndrome

In patients with Zollinger¬ Ellison syndrome the dosage should be individually adjusted and treatment continued as long as is clinically indicated. The recommended initial dosage is omeprazole 60 mg daily. All patients with severe disease and inadequate response to other therapies have been effectively controlled and more than 90% of the patients maintained on doses of omeprazole 20 - 120mg daily. When doses exceed omeprazole 80 mg daily, the dose should be divided and given twice daily.

Impaired renal function

Dose adjustment is not needed in patients with impaired renal function.

Impaired hepatic function

As bioavailability and plasma half-¬life of omeprazole are increased in patients with impaired hepatic function a daily dose of 10¬20 mg may be sufficient.

Elderly

Dose adjustment is not needed in the elderly.

Children

Promesec Capsule 20mg is not approved for use in children.

METHOD OF ADMINISTRATION

It is recommended to take Promesec Capsule 20mg in the morning, preferably without food, swallowed whole with half a glass of water. The capsules must not be chewed or crushed.

For patients with swallowing difficulties, patients can open the capsule and swallow the contents with half a glass of water or after mixing the contents in fruit juice, applesauce, or in non-carbonated water. Patients should be advised that the dispersion should be taken immediately (or within 30 minutes) and always be stirred just before drinking and rinsed down with half a glass of water. Alternatively patients can suck the capsule and swallow the pellets with half a glass of water. The enteric-coated pellets must not be chewed.

Route of administration: Oral

CONTRAINDICATIONS

Hypersensitivity to omeprazole, substituted benzimidazoles or to any of the excipients. Omeprazole like other proton pump inhibitors (PPIs) must not be used concomitantly with nelfinavir.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

In the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment may alleviate symptoms and delay diagnosis.

Co-administration of atazanavir with proton pump inhibitors is not recommended. If the combination of atazanavir with a proton pump inhibitor is judged unavoidable, close clinical monitoring (e.g virus load) is recommended in combination with an increase in the dose of atazanavir to 400 mg with 100 mg of ritonavir; omeprazole 20 mg should not be exceeded.

Vitamin B12 Deficiency

Daily treatment with any acid-suppressing medications over a long period of time (e.g. longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B12) caused by hypo- or achlorhydria. Rare reports of cyanocobalamin deficiency occurring with acid-suppressing therapy have been reported in the literature. This diagnosis should be considered if clinical symptoms consistent with cyanocobalamin deficiency are observed. The malabsorption should be considered in patients with reduced body stores or risk factors for reduced vitamin B12 absorption on long-term therapy

Omeprazole is a CYP2C19 inhibitor. When starting or ending treatment with omeprazole, the potential for interactions with drugs metabolised through CYP2C19 should be considered. As a precaution, concomitant use of omeprazole and clopidogrel should be discouraged.

Hypomagnesaemia

Severe hypomagnesaemia has been reported in patients treated with PPIs like omeprazole for at least three months, and in most cases for a year. Serious manifestations of hypomagnesaemia such as fatigue, tetany, delirium, convulsions, dizziness and ventricular arrhythmia can occur but they may begin insidiously and be overlooked. In most affected patients, hypomagnesaemia improved after magnesium replacement and discontinuation of the PPI.

For patients expected to be on prolonged treatment or who take PPIs with digoxin or drugs that may cause hypomagnesaemia (e.g. diuretics), healthcare professionals should consider measuring magnesium levels before starting PPI treatment and periodically during treatment.

Fracture

Proton pump inhibitors, especially if used in high doses and over long durations (>1 year), may modestly increase the risk of hip, wrist and spine fracture, predominantly in the elderly or in presence of other recognised risk factors. Observational studies suggest that proton pump inhibitors may increase the overall risk of fracture by 10- 40%. Some of this increase may be due to other risk factors. Patients at risk of osteoporosis should receive care according to current clinical guidelines and they should have an adequate intake of vitamin D and calcium.

Subacute cutaneous lupus erythematosus (SCLE)

Proton pump inhibitors are associated with very infrequent cases of subacute cutaneous lupus erythematosus (SCLE). If lesions occur, especially in sun-exposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and the healthcare professional should consider stopping omeprazole. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors.

Interference with laboratory tests

Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours.

If the patient(s) are due to have a test on Chromogranin A level, omeprazole treatment should be stopped for at least 5 days before CgA measurements to avoid this interference (see section Pharmacodynamics).

If CgA and gastrin levels have not returned to reference range after initial measurement, measurements should be repeated 14 days after cessation of proton pump inhibitor treatment.

Some children with chronic illnesses may require long-term treatment although it is not recommended.

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

Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter*.

Regular Surveillance

Patients on proton pump inhibitor treatment (particularly those treated for long term, especially when exceeding a treatment period of 1 year) should be kept under regular surveillance.

Clostridium Difficile Diarrhea

Published observational studies suggest that PPI therapy may be associated with an increased risk of Clostridium difficile associated diarrhea, especially in hospitalized patients. The diagnosis should be considered for diarrhea that does not improve. Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Active substances with pH dependent absorption

The decreased intragastric acidity during treatment with omeprazole might increase or decrease the absorption of active substances with a gastric pH dependent absorption.

Nelfinavir, atazanavir

The plasma levels of nelfinavir and atazanavir are decreased in case of co-administration with omeprazole. Concomitant administration of omeprazole with nelfinavir is contraindicated Co-administration of omeprazole (40 mg once daily) reduced mean nelvinavir exposure by ca. 40% and the mean exposure of the pharmacologically active metabolite M8 was reduced by ca. 75 –90%. The interaction may also involve CYP2C19 inhibition.

Concomitant administration of omeprazole with atazanavir is not recommended. Concomitant administration of omeprazole resulted in a decrease of atazanavir exposure.

Digoxin

Concomitant treatment with omeprazole and digoxin increased the bioavailability of digoxin. Digoxin toxicity has been rarely reported. However caution should be exercised when omeprazole is given at high doses in elderly patients. Therapeutic drug monitoring of digoxin should be then be reinforced.

Clopidogrel

A pharmacokinetic (PK)/pharmacodynamic (PD) interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and omeprazole (80mg p.o. daily) resulting in a decreased exposure to the active metabolite of clopidogrel and a decreased maximum inhibitionof (ADP induced) platelet aggregation. Inconsistent data on the clinical implications of a PK/PD interaction with clopidogrel in terms of major cardiovascular events have been reported from both observational and clinical studies.

Other active substances

The absorption of posaconazole, erlotinib, ketoconazole and itraconazole is significantly reduced and thus clinical efficacy may be impaired. For posaconazole and erlotinib concomitant use should be avoided.

Active substances metabolised by CYP2C19

Omeprazole is a moderate inhibitor of CYP2C19, the major omeprazole metabolising enzyme. Thus, the metabolism of concomitant active substances also metabolised by CYP2C19, may be decreased and the systemic exposure to these substances increased. Examples of such drugs are R-warfarin and other vitamin K antagonists, cilostazol, diazepam and phenytoin.

Cilostazol

Omeprazole increased the C_{MAX} and AUC for cilostazol

Phenytoin

Monitoring phenytoin plasma concentration is recommended during the first two weeks after initiating omeprazole treatment and, if a phenytoin dose adjustment is made, monitoring and a further dose adjustment should occur upon ending omeprazole treatment.

Unknown Mechanism

Saquinavir

Concomitant administration of omeprazole with saquinavir/ritonavir resulted in increased plasma levels up to approximately 70% for saquinavir associated with good tolerability in HIV-infected patients.

Tacrolimus

Concomitant administration of omeprazole has been reported to increase the serum levels of tacrolimus. A reinforced monitoring of tacrolimus concentrations as well as renal function (creatinine clearance) should be performed, and dosage of tacrolimus adjusted if needed.

Methotrexate

When given together with proton-pump inhibitors, methotrexate levels have been reported to increase in some patients. In high-dose methotrexate administration a temporary withdrawal of omeprazole may need to be considered.

Inhibitors CYP2C19 and/or CYP3A4

Since omeprazole is metabolised by CYP2C19 and CYP3A4, active substances known to inhibit CYP2C19 or CYP3A4 (such as clarithromycin and voriconazole) may lead to increased omeprazole serum levels by decreasing omeprazole's rate of metabolism. Concomitant voriconazole treatment resulted in more than doubling of the omeprazole exposure. As high doses of omeprazole have been well-tolerated adjustment of the omeprazole dose is not generally required. However, dose adjustment should be considered in patients with severe hepatic impairment and if long-term treatment is indicated.

Inducers of CYP2C19 and/or CYP3A4
Active substances known to induce CYP2C19 or CYP3A4 or both (such as rifampicin and St John's wort) may lead to decreased omeprazole serum levels by increasing omeprazole's rate of metabolism.

PREGNANCY AND LACTATION
Results from three prospective epidemiological studies (more than 1000 exposed outcomes) indicate no adverse effects of omeprazole on pregnancy or on the health of the foetus/newborn child. Omeprazole can be used during pregnancy.
Omeprazole is excreted in breast milk but is not likely to influence the child when therapeutic doses are used.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
Omeprazole is not likely to affect the ability to drive or use machines. Adverse drug reactions such as dizziness and visual disturbances may occur If affected, patients should not drive or operate machinery.

UNDESIRABLE EFFECTS
The most common side effects are headache, abdominal pain, constipation, diarrhoea, flatulence and nausea/vomiting. The following adverse drug reactions are not dose-related and are classified according to frequency and System Organ Class (SOC). Frequency categories are defined according to the following convention: Very common, Common, Uncommon, Rare, Very rare, Not known.

System	Adverse reaction
Blood and lymphatic system disorders	
Rare	Leukopenia, thrombocytopenia
Very Rare	Agranulocytosis, pancytopenia
Immune system disorders	
Rare	Hypersensitivity reactions e.g. fever, angioedema and anaphylactic reaction/shock
Metabolism and nutrition disorders	
Rare	Hyponatraemia
Not Known	Hypomagnesaemia
	Vitamin B12 deficiency
Psychiatric disorders	
Uncommon	Insomnia
Rare	Agitation, confusion, depression
Very Rare	Aggression, hallucinations
Nervous system disorders	
Common	Headache
Uncommon	Dizziness, paraesthesia, somnolence
Rare	Taste disturbance
Eye disorders	
Rare	Blurred vision
Ear and labyrinth disorders	
Uncommon	Vertigo
Respiratory, thoracic and mediastinal disorders	
Rare	Bronchospasm
Gastrointestinal disorders	
Common	Abdominal pain, constipation, diarrhoea, flatulence, nausea/vomiting, fundic gland polyps (benign)
Rare	Dry mouth, stomatitis, gastrointestinal candidiasis, microscopic colitis
Not known	Microscopic colitis
Hepatobiliary disorders	
Uncommon	Increased liver enzymes
Rare	Hepatitis with or without jaundice
Very Rare	Hepatic failure, encephalopathy in patients with pre-existing liver disease
Skin and subcutaneous tissue disorders	
Uncommon	Dermatitis, pruritus, rash, urticaria
Rare	Alopecia, photosensitivity
Very Rare	Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN)
Not known	Subacute cutaneous lupus erythematosus
Musculoskeletal and connective tissue disorders	
Rare	Arthralgia, myalgia
Very Rare	Muscular weakness
Uncommon	Fracture of the hip, wrist or spine
Renal and urinary disorders	
	Interstitial nephritis
Reproductive system and breast disorders	
Very Rare	Gynaecomastia
General disorders and administration site conditions	
Uncommon	Malaise, peripheral oedema
Rare	Increased sweating
Infection and Infestations	
	Clostridium difficile associated diarrhea

Paediatric population
The adverse event profile was generally the same as for adults in short- as well as in long-term treatment. There are no long-term data regarding the effects of omeprazole treatment on puberty and growth.

SYMPTOMS AND TREATMENT OF OVERDOSE
There is limited information available on the effects of overdoses of omeprazole in humans. In the literature, doses of up to 560 mg have been described, and occasional reports have been received when single oral doses have reached up to 2,400 mg omeprazole (120 times the usual recommended clinical dose) . Nausea, vomiting, dizziness, abdominal pain, diarrhoea and headache have been reported. Also apathy, depression and confusion have been described in single cases. The symptoms described have been transient, and no serious outcome has been reported. The rate of elimination was unchanged (first order kinetics) with increased doses. Treatment, if needed, is symptomatic.

PHARMACODYNAMICS
Mechanism of action
Omeprazole, a racemic mixture of two enantiomers reduces gastric acid secretion through a highly targeted mechanism of action. It is a specific inhibitor of the acid pump in the parietal cell. It is rapidly acting and provides control through reversible inhibition of gastric acid secretion with once daily dosing. Omeprazole is a weak base and is concentrated and converted to the active form in the highly acidic environment of the intracellular canaliculi within the parietal cell, where it inhibits the enzyme H+ K+-ATPase - the acid pump. This effect on the final step of the gastric acid formation process is dose-dependent and provides for highly effective inhibition of both basal acid secretion and stimulated acid secretion, irrespective of stimulus.
Effect on gastric acid secretion
Oral dosing with omeprazole once daily provides for rapid and effective inhibition of daytime and night-time gastric acid secretion with maximum effect being achieved within 4 days of treatment. As a consequence of reduced acid secretion and intragastric acidity, omeprazole dose dependently reduces/normalizes acid exposure of the esophagus in patients with gastroesophageal reflux disease. The inhibition of acid secretion is related to the area under the plasma concentration-time curve (AUC) of omeprazole and not to the actual plasma concentration at a given time.

Effect on H. pylori
H. pylori is associated with peptic ulcer disease, including duodenal and gastric ulcer disease. H. pylori is a major factor in the development of gastritis. H. pylori together with gastric acid are major factors in the development of peptic ulcer disease. H. pylori is a major factor in the development of atrophic gastritis which is associated with an increased risk of developing gastric cancer. Eradication of H. pylori with omeprazole and antimicrobials is associated with high rates of healing and long-term remission of peptic ulcers. Dual therapies have been tested and found to be less effective than triple therapies. They could, however, be considered in cases where known hypersensitivity precludes use of any triple combination.
Other effects related to acid inhibition
During long-term treatment gastric glandular cysts have been reported in a somewhat increased frequency. These changes are a physiological consequence of pronounced inhibition of acid secretion, are benign and appear to be reversible. Decreased gastric acidity due to any means including proton pump inhibitors, increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with acid-reducing drugs may lead to slightly increased risk of gastrointestinal infections such as Salmonella and Campylobacter. During treatment with antisecretory medicinal products serum gastrin increases in response to the decreased acid secretion. Also CgA increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours. Available published evidence suggests that proton pump inhibitor treatment should be discontinued between 5 days and 2 weeks prior to CgA measurement. This is to allow CgA levels that might be spuriously elevated following PPI treatment to return to reference range An increased number of ECL cells possibly related to the increased serum gastrin levels, have been observed in some patients (both children and adults) during long term treatment with omeprazole. The findings are considered to be of no clinical significance.

PHARMACOKINETICS
Absorption
Omeprazole and omeprazole magnesium are acid labile and are therefore administered orally as enteric-coated granules in capsules or tablets. Absorption of omeprazole is rapid, with peak plasma levels occurring approximately 1-2 hours after dose. Absorption of omeprazole takes place in the small intestine and is usually completed within 3-6 hours.
Concomitant intake of food has no influence on the bioavailability. The systemic availability (bioavailability) from a single oral dose of omeprazole is approximately 40%.
After repeated once-daily administration, the bioavailability increases to about 60%.
Distribution
Omeprazole is 97% plasma protein bound.
Metabolism
Omeprazole is completely metabolised by the cytochrome P450 system (CYP). The major part of its metabolism is dependent on the polymorphically expressed CYP2C19, responsible for the formation of hydroxyomeprazole, the major metabolite in plasma. The remaining part is dependent on another specific isoform, CYP3A4, responsible for the formation of omeprazole sulphone. As a consequence of high affinity of omeprazole to CYP2C19, there is a potential for competitive inhibition and metabolic drug-drug interactions with other substrates for CYP2C19. However, due to low affinity to CYP3A4, omeprazole has no potential to inhibit the metabolism of other CYP3A4 substrates. In addition, omeprazole lacks an inhibitory effect on the main CYP enzymes. In poor metabolizers the metabolism of omeprazole is probably mainly catalysed by CYP3A4.
Excretion
The plasma elimination half-life of omeprazole is usually shorter than one hour both after single and repeated oral once-daily dosing. Omeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration.
Almost 80% of an oral dose of omeprazole is excreted as metabolites in the urine, the remainder in the faeces, primarily originating from bile secretion.
The AUC of omeprazole increases with repeated administration. This increase is dose dependent and results in a non-linear dose-AUC relationship after repeated administration.
This time- and dose-dependency is due to a decrease of first pass metabolism and systemic clearance probably caused by an inhibition of the CYP2C19 enzyme by omeprazole and/or its metabolites (e.g. the sulphone).
No metabolite has been found to have any effect on gastric acid secretion.
Special Populations.
Impaired hepatic function
The metabolism of omeprazole in patients with liver dysfunction is impaired, resulting in an increased AUC. Omeprazole has not shown any tendency to accumulate with once daily dosing.
Impaired renal function
The pharmacokinetics of omeprazole, including systemic bioavailability and elimination rate, are unchanged in patients with reduced renal function.
Elderly
The metabolism rate of omeprazole is somewhat reduced in elderly aged 75-79 years.
Paediatric patients
During treatment with the recommended doses to children from the age of 1 year, plasma concentrations are comparable to adults. In children younger than 6 months, clearance of omeprazole is low due to low capacity to metabolise omeprazole.

PRODUCT DESCRIPTION
Reddish brown cap / Pink body size '2' hard gelatin capsule imprinted with 'H' on cap and 'O2' on body, filled with white to off white pellets.

DOSAGE FORM AND PACKAGING AVAILABLE
Blister Pack: 1 x 7's, 2 x 7's, 4 x 7's, 12 x 7's 24 x 7's Alu- Alu

STORAGE CONDITION
Store below 30°C.
Keep out of reach of children. Jauhkan daripada capaian kanak-kanak.

MANUFACTURER
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PRODUCT REGISTRATION HOLDER
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Lot No. 2, 4, 6, 8 & 10,
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Bandar Baru Bangi,
Selangor, Malaysia.

Revision Date: Sept 2019

Size: 210x300 mm
Pre-Fold: 105x 30 mm
Spec: 40 gsm Bible paper, Front & Back Printing Colour: 1 (Black)
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