

# NEW ZEALAND DATA SHEET

## 1. PRODUCT NAME

MAREVAN Warfarin sodium Tablets 1 mg, 3 mg and 5 mg

MAREVAN Warfarin sodium Tablets are not substitutable for any other warfarin product as if the two products were bioequivalent.

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

MAREVAN Tablet 1 mg: Each tablet contains 1 mg warfarin sodium.

MAREVAN Tablet 3 mg: Each tablet contains 3 mg warfarin sodium.

MAREVAN Tablet 5 mg: Each tablet contains 5 mg warfarin sodium.

For the full list of excipients, see section 6.1 List of excipients.

## 3. PHARMACEUTICAL FORM

Tablet

MAREVAN Tablet 1 mg: brown uncoated round flat bevelled edge tablet, 8 mm in diameter and 2 mm deep, engraved DF/M1 on one side.

MAREVAN Tablet 3 mg: pale blue uncoated round flat bevelled edge tablet, 8 mm in diameter and 2 mm deep, engraved DF/M3 on one side.

MAREVAN Tablet 5 mg: pink uncoated round flat bevelled edge tablet, 8 mm in diameter and 2 mm deep, engraved DF/M5 on one side.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

Coronary occlusion; deep vein thrombosis; pulmonary embolism; peripheral vascular thromboembolic states; mesenteric and retinal thromboembolism.

In emergencies, such as the conditions listed above, anticoagulant therapy should be initiated with heparin and MAREVAN together. Where there is less urgency, as in patients disposed to or at special risk of thromboembolism, anticoagulant therapy may be initiated with MAREVAN alone. Appropriate indications include predisposition to thromboembolism following surgery and chronic embolic pulmonary hypertensive disease.

### 4.2 Dosage and method of administration

#### Dose

10 to 15 mg daily, according to age and body weight, and adjusted with relation to the results of daily control tests until the desired level of anticoagulant activity is achieved - usually three to six days after the initiation of treatment.

Control tests should be made at regular intervals and the MAREVAN maintenance dosage must be adjusted according to the results obtained.

Concomitant heparin therapy affects the results of control tests and should be discontinued at least six hours before the first test is carried out.

In emergencies, anticoagulant therapy should be initiated with heparin and warfarin together. Where there is less urgency, as in patients disposed to or at special risk of thromboembolism, anticoagulant therapy may be initiated with warfarin alone.

### Children

Infants, especially neonates, may be more sensitive to the effects of anticoagulants in general, due to vitamin K deficiency.

### Elderly

The elderly may be more susceptible to the effects of warfarin, resulting in increased risk of haemorrhage. Lower maintenance doses, weight for weight, than those usually recommended for adults may be required for these patients.

## **4.3 Contraindications**

Warfarin is contraindicated in:

- known hypersensitivity to warfarin or to any of the excipients
- haemorrhagic stroke
- clinically significant bleeding
- within 72 hours of major surgery with risk of severe bleeding
- within 48 hours postpartum
- pregnancy (first and third trimesters, see section 4.6 Fertility, pregnancy and lactation)
- concomitant use of fibrinolytic drugs such as streptokinase and alteplase and drugs where interactions may lead to a significantly increased risk of bleeding (see section 4.5 Interaction with other medicines and other forms of interaction).

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

### Adverse Events

Most adverse events reported with warfarin are a result of over anticoagulation therefore it is important that the need for therapy is reviewed on a regular basis and therapy discontinued when no longer required.

## Monitoring

When warfarin is started using a standard dosing regimen the INR should be determined daily or on alternate days in the early days of treatment. Once the INR has stabilised in the target range the INR can be determined at longer intervals.

INR should be monitored more frequently in patients at an increased risk of over coagulation e.g. patients with severe hypertension, liver or renal disease.

Patients for whom adherence may be difficult should be monitored more frequently.

## Thrombophilia

Patients with protein C deficiency are at risk of developing skin necrosis when starting warfarin treatment. In patients with protein C deficiency, therapy should be introduced without a loading dose of warfarin even if heparin is given. Patients with protein S deficiency may also be at risk and it is advisable to introduce warfarin therapy slowly in these circumstances.

## Risk of Haemorrhage

The most frequently reported adverse effect of all oral anticoagulants is haemorrhage. Warfarin should be given with caution to patients where there is a risk of serious haemorrhage (e.g. concomitant NSAID use, recent ischaemic stroke, bacterial endocarditis, previous gastrointestinal bleeding).

Risk factors for bleeding include high intensity of anticoagulation (INR >4.0), age  $\geq 65$ , highly variable INRs, history of gastrointestinal bleeding, uncontrolled hypertension, cerebrovascular disease, serious heart disease, risk of falling, anaemia, malignancy, trauma, renal insufficiency, concomitant drugs (see section 4.5 Interaction with other medicines and other forms of interaction).

All patients treated with warfarin should have INR monitored regularly. Those at high risk of bleeding may benefit from more frequent INR monitoring, careful dose adjustment to desired INR, and a shorter duration of therapy. Patients should be instructed on measures to minimise risk of bleeding and to report immediately to physicians signs and symptoms of bleeding.

Checking the INR and reducing or omitting doses depending on INR level is essential, following consultation with anticoagulation services if necessary. If the INR is found to be too high, reduce dose or stop warfarin treatment; sometimes it will be necessary to reverse anticoagulation. INR should be checked within 2–3 days to ensure that it is falling.

Any concomitant anti-platelet drugs should be used with caution due to an increased risk of bleeding.

## Haemorrhage

Haemorrhage can indicate an overdose of warfarin has been taken. For advice on treatment of haemorrhage see section 4.9 Overdose.

Unexpected bleeding at therapeutic levels should always be investigated and INR monitored.

### Ischaemic Stroke

Anticoagulation following an ischaemic stroke increases the risk of secondary haemorrhage into the infarcted brain. In patients with atrial fibrillation long term treatment with warfarin is beneficial, but the risk of early recurrent embolism is low and therefore a break in treatment after ischaemic stroke is justified. Warfarin treatment should be re-started 2–14 days following ischaemic stroke, depending on the size of the infarct and blood pressure. In patients with large embolic strokes, or uncontrolled hypertension, warfarin treatment should be stopped for 14 days.

### Surgery

For surgery where there is no risk of severe bleeding, surgery can be performed with an INR of <2.5.

For surgery where there is a risk of severe bleeding, warfarin should be stopped 3 days prior to surgery.

Where it is necessary to continue anticoagulation e.g. risk of life-threatening thromboembolism, the INR should be reduced to <2.5 and heparin therapy should be started.

If surgery is required and warfarin cannot be stopped 3 days beforehand, anticoagulation should be reversed with low-dose vitamin K.

The timing for re-instating warfarin therapy depends on the risk of post-operative haemorrhage. In most instances warfarin treatment can be re-started as soon as the patient has an oral intake.

### Dental Surgery

Warfarin need not be stopped before routine dental surgery, e.g., tooth extraction.

### Active Peptic Ulceration

Due to a high risk of bleeding, patients with active peptic ulcers should be treated with caution. Such patients should be reviewed regularly and informed of how to recognise bleeding and what to do in the event of bleeding occurring.

### Interactions

Many drugs and foods interact with warfarin and affect the prothrombin time (see section 4.5 Interaction with other medicines and other forms of interaction). Any change to medication, including self-medication with OTC products, warrants increased monitoring of the INR. Patients should be instructed to inform their doctor before they start to take any additional medications including over the counter medicines, herbal remedies or vitamin preparations.

### Thyroid Disorders

The rate of warfarin metabolism depends on thyroid status. Therefore patients with hyper- or hypo-thyroidism should be closely monitored on starting warfarin therapy.

### Calciphylaxis

Calciphylaxis is a rare syndrome of vascular calcification with cutaneous necrosis, associated with high mortality. The condition is mainly observed in patients with end-stage renal disease on dialysis or in patients with known risk factors such as protein C or S deficiency, hyperphosphataemia, hypercalcaemia or hypoalbuminaemia. Rare cases of calciphylaxis have been reported in patients taking warfarin, also in the absence of renal disease. In case calciphylaxis is diagnosed, appropriate treatment should be started and consideration should be given to stopping treatment with warfarin.

### Additional Circumstances Where Changes in Dose May be Required

The following also may exaggerate the effect of warfarin tablets, and necessitate a reduction of dosage:

- loss of weight
- acute illness
- cessation of smoking.

The following may reduce the effect of warfarin tablets, and require the dosage to be increased:

- weight gain
- diarrhoea
- vomiting.

### Warfarin Resistance

Acquired or inherited warfarin resistance should be suspected if larger than usual daily doses of warfarin are required to achieve the desired anticoagulant effect.

### Genetic Information

Genetic variability particularly in relation to CYP2C9 and VKORC1 can significantly affect dose requirements for warfarin. If a family association with these polymorphisms is known extra care is warranted.

### Lactose

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

## **4.5 Interaction with other medicines and other forms of interaction**

### Narrow therapeutic range

Warfarin has a narrow therapeutic range and care is required with all concomitant therapy. The individual product information for any new concomitant therapy should be consulted for specific guidance on warfarin dose adjustment and therapeutic monitoring. If no information is provided the possibility of an interaction should be

considered. Increased monitoring should be considered when commencing any new therapy if there is any doubt as to the extent of interaction.

### Pharmacodynamic interactions

#### *Drugs which are contraindicated*

Concomitant use of drugs used in the treatment or prophylaxis of thrombosis, or other drugs with adverse effects on haemostasis may increase the pharmacological effect of warfarin, increasing the risk of bleeding.

Fibrinolytic drugs such as streptokinase and alteplase are contraindicated in patients receiving warfarin (see section 4.3 Contraindications).

#### *Drugs which should be avoided if possible*

The following examples should be avoided, or administered with caution with increased clinical and laboratory monitoring:

- clopidogrel
- NSAIDs (including aspirin and cox-2 specific NSAIDs)
- sulfinpyrazone
- thrombin inhibitors such as bivalirudin, dabigatran
- dipyridamole
- unfractionated heparins and heparin derivatives, low molecular weight heparins
- fondaparinux, rivaroxaban
- glycoprotein IIb/IIIa receptor antagonists such as eptifibatide, tirofiban and abciximab
- prostacyclin
- SSRI and SNRI antidepressants
- other drugs which inhibit haemostasis, clotting or platelet action

#### *Low-dose aspirin*

Low-dose aspirin with warfarin may have a role in some patients but the risk of gastrointestinal bleeding is increased. Warfarin may initially be given with a heparin in the initial treatment of thrombosis, until the INR is in the correct range.

### Metabolic interactions

Warfarin is a mixture of enantiomers which are metabolised by different CYP450 cytochromes. R-warfarin is metabolised primarily by CYP1A2 and CYP3A4. S-warfarin is metabolised primarily by CYP2C9. The efficacy of warfarin is affected primarily when the metabolism of S-warfarin is altered.

Drugs that compete as substrates for these cytochromes or inhibit their activity may increase warfarin plasma concentrations and INR, potentially increasing the risk of bleeding. When these drugs are co-administered, warfarin dosage may need to be reduced and the level of monitoring increased.

Conversely, drugs which induce these metabolic pathways may decrease warfarin plasma concentrations and INR, potentially leading to reduced efficacy. When these drugs are co-administered, warfarin dosage may need to be increased and the level of monitoring increased.

There is a small subset of drugs for which interactions are known, however their clinical effect on the INR is variable; in these cases increased monitoring on starting and stopping therapy is advised.

Care should also be taken when stopping or reducing the dose of a metabolic inhibitor or inducer, once patients are stable on this combination (offset effect).

Listed below are drugs which are known to interact with warfarin in a clinically significant way.

#### *Examples of drugs which potentiate the effect of warfarin*

- allopurinol, capecitabine, erlotinib, disulfiram, azole antifungals (ketoconazole, fluconazole etc),
- omeprazole, paracetamol (prolonged regular use), propafenone, amiodarone, tamoxifen, methylphenidate,
- zafirlukast, fibrates, statins (not pravastatin, predominantly associated with fluvastatin),
- erythromycin, sulfamethoxazole, metronidazole.

#### *Examples of drugs which antagonise the effect of warfarin*

- barbiturates,
- primidone, carbamazepine,
- griseofulvin, oral contraceptives,
- rifampicin, azathioprine, phenytoin.

#### *Examples of drugs with variable effect*

- corticosteroids, nevirapine, ritonavir.

#### Other interactions

##### *Antibiotics and orlistat*

Broad spectrum antibiotics may potentiate the effect of warfarin by reducing the gut flora which produce vitamin K. Similarly, orlistat may reduce absorption of vitamin K.

### *Cholestyramine and sucralfate*

Cholestyramine and sucralfate potentially decrease absorption of warfarin.

### *Direct-acting antivirals (DAAV)*

As liver function may change during treatment with direct-acting antivirals such as boceprevir, daclatasvir, dasabuvir, elbasvir, grazoprevir, ledipasvir, sofosbuvir, ombitasvir, paritaprevir, simeprevir, velpatasvir, a close monitoring of INR values is recommended.

### *Glucosamine*

Increased INR has been reported in patients taking glucosamine and oral vitamin K antagonists. Patients treated with oral vitamin K antagonists should therefore be closely monitored at the time of initiation or termination of glucosamine therapy.

### *Interactions with herbal products*

Herbal preparations containing St John's Wort (*Hypericum perforatum*) must not be used whilst taking warfarin due to a proven risk of decreased plasma concentrations and reduced clinical effects of warfarin.

Many other herbal products have a theoretical effect on warfarin; however most of these interactions are not proven. Patients should generally avoid taking any herbal medicines or food supplements whilst taking warfarin, and should be told to advise their doctor if they are taking any, as more frequent monitoring is advisable.

### *Alcohol*

Acute ingestion of a large amount of alcohol may inhibit the metabolism of warfarin and increase INR.

Conversely, chronic heavy alcohol intake may induce the metabolism of warfarin.

Moderate alcohol intake can be permitted.

### *Interactions with food and food supplements*

Individual case reports suggest a possible interaction between warfarin and cranberry juice, in most cases leading to an increase in INR or bleeding event. Patients should be advised to avoid cranberry products. Increased supervision and INR monitoring should be considered for any patient taking warfarin and regular cranberry juice.

Limited evidence suggests that grapefruit juice may cause a modest rise in INR in some patients taking warfarin.

Certain foods such as liver, broccoli, brussels sprouts and green leafy vegetables contain large amounts of vitamin K. Sudden changes in diet can potentially affect control of anticoagulation. Patients should be informed of the need to seek medical advice before undertaking any major changes in diet.

Many other food supplements have a theoretical effect on warfarin; however most of these interactions are not proven. Patients should generally avoid taking any food



supplements whilst taking warfarin, and should be told to advise their doctor if they are taking any, as more frequent monitoring is advisable.

#### *Laboratory tests*

Heparins and danaparoid may prolong the prothrombin time, therefore a sufficient time interval should be allowed after administration before performing the test.

### **4.6 Fertility, pregnancy and lactation**

#### Pregnancy

Warfarin is contraindicated in pregnancy in the first and third trimester (see section 4.3 Contraindications).

Based on human experience warfarin causes congenital malformations and foetal death when administered during pregnancy.

Women of child-bearing age who are taking warfarin tablets should use effective contraception during treatment.

#### Breastfeeding

Warfarin can be used during breast-feeding. Warfarin is excreted in breast milk in small amounts. However, at therapeutic doses of warfarin no effects on the breastfed child are anticipated.

#### Fertility

There are no relevant data available.

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

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

### **4.8 Undesirable effects**

#### Clinical Trial Data

There are no relevant data available.

#### Post Marketing Data

Adverse drug reactions (ADRs) are listed below by MedDRA system organ class and by frequency.

Frequencies are defined as:

|             |  |
|-------------|--|
| Very common | $\geq 1/10$                                    |
| Common      | $\geq 1/100$ to $< 1/10$                       |
| Uncommon    | $\geq 1/1000$ to $< 1/100$                     |
| Rare        | $\geq 1/10000$ to $< 1/1000$                   |
| Very rare   | $< 1/10000$                                    |
| Not known   | (cannot be estimated from the available data). |

### Blood and lymphatic system disorders

*Not known:* haematocrit decreased, haemoglobin decreased

### Immune system disorders

*Not known:* hypersensitivity

### Nervous system disorders

*Not known:* cerebral haemorrhage, cerebral subdural haematoma

### Vascular disorders

*Not known:* haemorrhage, purple toes syndrome

### Respiratory, thoracic and mediastinal disorders

*Not known:* haemothorax, epistaxis

### Gastrointestinal disorders

*Not known:* gastrointestinal haemorrhage, rectal haemorrhage, haematemesis, pancreatitis, diarrhoea, nausea, vomiting, melaena

### Hepatobiliary disorders

*Not known:* jaundice, hepatic dysfunction

### Skin and subcutaneous tissue disorders

*Not known:* rash, alopecia, purpura, erythematous swollen skin patches leading to ecchymosis, infarction and skin necrosis, calciphylaxis

### Renal and urinary disorders

*Not known:* haematuria

### General disorders and administration site conditions

*Not known:* pyrexia

### Haemorrhage

Haemorrhage from any tissue or organ. This is a consequence of the anticoagulant effect. The signs and symptoms will vary according to the location and degree or extent of the bleeding. Haemorrhagic complications may present as paralysis; headache, chest, abdomen, joint or other pain; shortness of breath, difficult breathing or swallowing; unexplained swelling; or unexplained shock.

Therefore, the possibility of haemorrhage should be considered in evaluating the condition of any anticoagulated patient with complaints which do not indicate an obvious diagnosis. Bleeding during anticoagulant therapy does not always correlate with prothrombin activity. (see section 4.9 - Overdose)

Bleeding which occurs when the prothrombin time is within the therapeutic range warrants diagnostic investigation since it may unmask a previously unsuspected lesion e.g. tumour, ulcer, etc.

#### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions via: <https://nzphvc.otago.ac.nz/reporting>

### **4.9 Overdose**

#### Treatment

If the patient presents within 1 hour of ingestion of more than 0.25 mg/kg or more than the patient's therapeutic dose, consider activated charcoal (50 g for adults; 1 g/kg for children)

#### *In cases of life-threatening haemorrhage*

Stop warfarin treatment, give prothrombin complex concentrate (factors II, VII, IX, and X) 30-50 units/kg *or* (if no concentrate available) fresh frozen plasma 15 mL/kg.

#### *Non-life threatening haemorrhage*

Where anticoagulation can be suspended, give slow intravenous injection of phytomenadione (vitamin K<sub>1</sub>) 10-20 mg for adults (250 micrograms/kg for a child)

Where rapid re-anticoagulation is desirable (e.g., valve replacements) give prothrombin complex concentrate (factors II, VII, IX, and X) 30-50 units/kg *or* (if no concentrate available) fresh frozen plasma 15 mL/kg.

Monitor INR to determine when to restart normal therapy. Monitor INR for at least 48 hours post overdose.

#### *Patients on long-term warfarin therapy without major haemorrhage*

- INR >8.0, no bleeding or minor bleeding-stop warfarin, and give phytomenadione (vitamin K<sub>1</sub>) 0.5-1 mg for adults, 0.015-0.030 mg/kg (15-30 micrograms/kg) for children by slow intravenous injection or 5 mg by mouth (for partial reversal of anticoagulation give smaller oral doses of phytomenadione eg, 0.5-2.5 mg using the intravenous preparation orally); repeat dose of phytomenadione if INR still too high after 24 hours. Large doses of phytomenadione may completely reverse the effects of warfarin and make re-establishment of anticoagulation difficult.
- INR 6.0-8.0, no bleeding or minor bleeding-stop warfarin, restart when INR <5.0
- INR <6.0 but more than 0.5 units above target value-reduce dose or stop warfarin, restart when INR <5.0

#### *For patients NOT on long-term anticoagulants without major haemorrhage*

Measure the INR (prothrombin time) at presentation and sequentially every 24-48 hours after ingestion depending on the initial dose and initial INR.

- If the INR remains normal for 24-48 hours and there is no evidence of bleeding, there should be no further monitoring necessary.
  - Give vitamin K<sub>1</sub> (phytomenadione) if:
    - a) there is no active bleeding and the patient has ingested more than 0.25 mg/kg;
- OR
- b) the prothrombin time is already significantly prolonged (INR >4.0).

The adult dose of vitamin K<sub>1</sub> is 10-20 mg orally (250 micrograms/kg body weight for a child). Delay oral vitamin K<sub>1</sub> at least 4 hours after any activated charcoal has been given. Repeat INR at 24 hours and consider further vitamin K<sub>1</sub>.

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

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: antithrombotic agent – Vitamin K antagonist, ATC code: B01A A03

#### Mechanism of action

MAREVAN is a synthetic 4-hydroxycoumarin derivative which acts by preventing the formation of active procoagulation factors II, VII, IX and X in the liver by inhibiting the vitamin K-mediated gamma-carboxylation of precursor proteins. Full therapeutic activity is not achieved until circulating coagulation factors have been removed by normal catabolism. This occurs at different rates for each factor, with factor VII having the shortest half-life. Warfarin has no direct thrombolytic effect, though it may limit the extension of existing thrombi.

### **5.2 Pharmacokinetic properties**

#### Absorption

Warfarin sodium is readily absorbed from the gastro-intestinal tract.

#### Distribution

Warfarin is extensively bound to plasma proteins and its plasma half-life is about 40 hours. The time to reach peak plasma concentration is 24 to 48 hours.

#### Biotransformation

Warfarin sodium is metabolised in the liver. The metabolites of warfarin sodium include 7-hydroxywarfarin, 6-hydroxywarfarin and two warfarin alcohols. These are all inactive. Warfarin crosses the placenta.

### Elimination

Warfarin sodium is metabolised in the liver and is excreted in the urine, mainly as metabolites.

### Special patient populations

#### Renal impairment

Renal damage may reduce the rate of excretion of warfarin and thus decrease the dose requirement (see section 4.4 Special warnings and precautions for use).

Patients with nephrotic syndrome may require a higher dose of warfarin; this may be due to a shortened half-life of the anticoagulant caused by proteinuria and excretion of medicine bound to albumin.

#### Hepatic impairment

In the presence of hepatic dysfunction, there may be impaired metabolism of warfarin and/or impaired synthesis of clotting factors.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of Excipients**

The 1 mg, 3 mg and 5 mg tablets contain the following excipients:

- Lactose monohydrate
- Magnesium stearate
- Maize starch
- Pregelatinised maize starch
- Sodium starch glycolate

The 1 mg tablets also contain the colourants:

- Indigo carmine
- Iron oxide red
- Iron oxide yellow

The 3 mg tablets also contain the colourant:

- Indigo carmine

The 5 mg tablets also contain the colourant:

- Erythrosine

MAREVAN tablets contain lactose.

### **6.2 Incompatibilities**

There are no relevant data available

### **6.3 Shelf life**

2 years

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

Store at room temperature (below 25°C).

Replace cap securely and protect from light.

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

Marevan tablets are packed in a polypropylene bottle containing 100 tablets.

### **6.6 Special precautions for disposal**

No special requirements for disposal.

## **7. MEDICINE SCHEDULE**

Prescription Medicine

## **8. SPONSOR**

GlaxoSmithKline NZ Limited

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New Zealand

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## **9. DATE OF FIRST APPROVAL**

Date of publication in the New Zealand Gazette of consent to distribute the medicine:  
31 December 1969

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

18 October 2022

Summary table of changes:

| <b>Section changed</b> | <b>Summary of new information</b>    |
|------------------------|--------------------------------------|
| 4.8                    | Inclusion of haemorrhage information |

Version 10.0

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