

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Famciclovir Teva 250 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 250 mg of famciclovir.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

White to off-white, round, film-coated tablets, engraved 8118 on one side and 93 on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Varicella zoster virus (VZV) infections – herpes zoster

Famciclovir is indicated for

- the treatment of herpes zoster and ophthalmic zoster in immunocompetent adults (see section 4.4).
- the treatment of herpes zoster in immunocompromised adults (see section 4.4).

Herpes simplex virus (HSV) infections – genital herpes

Famciclovir is indicated for

- the treatment of first and recurrent episodes of genital herpes in immunocompetent adults.
- the treatment of recurrent episodes of genital herpes in immunocompromised adults.
- the suppression of recurrent genital herpes in immunocompetent and immunocompromised adults.

Clinical studies have not been conducted in HSV-infected patients immunocompromised for other causes than HIV infection (see section 5.1).

4.2 Posology and method of administration

Posology

Herpes zoster and ophthalmic zoster in immunocompetent adults

500 mg three times daily for seven days.

Treatment should be initiated as soon as possible after a diagnosis of herpes zoster or ophthalmic zoster.

Herpes zoster in immunocompromised adults

500 mg three times daily for ten days.

Treatment should be initiated as soon as possible after a diagnosis of herpes zoster.

Genital herpes in immunocompetent adults

First episode of genital herpes: 250 mg three times daily for five days. Initiation of treatment is recommended as soon as possible after a diagnosis of first episode of genital herpes.

Episodic treatment of recurrent genital herpes: 125 mg twice daily for five days. Initiation of treatment is recommended as soon as possible after onset of prodromal symptoms (e.g. tingling, itching, burning, pain) or lesions.

Recurrent genital herpes in immunocompromised adults

Episodic treatment of recurrent genital herpes: 500 mg twice daily for seven days. Initiation of treatment is recommended as soon as possible after onset of prodromal symptoms (e.g. tingling, itching, burning, pain) or lesions.

Suppression of recurrent genital herpes in immunocompetent adults

250 mg twice daily. Suppressive therapy should be discontinued after a maximum of 12 months of continuous antiviral therapy to reassess recurrence frequency and severity. The minimum period of reassessment should include two recurrences. Patients who continue to have significant disease may restart suppressive therapy.

Suppression of recurrent genital herpes in immunocompromised adults

500 mg twice daily.

Patients with renal impairment

Because reduced clearance of penciclovir is related to reduced renal function, as measured by creatinine clearance, special attention should be given to doses in patients with impaired renal function. Dose recommendations for adult patients with renal impairment are provided in Table 1.

Table 1: Dose recommendations for adult patients with renal impairment

| Indication and nominal dose regimen | Creatinine clearance [ml/min] | Adjusted dose regimen |
|--|--------------------------------------|--|
| Herpes zoster in immunocompetent adults | | |
| 500 mg three times daily for 7 days | ≥60 | 500 mg three times daily for 7 days |
| | 40 to 59 | 500 mg twice daily for 7 days |
| | 20 to 39 | 500 mg once daily for 7 days |
| | <20 | 250 mg once daily for 7 days |
| | Haemodialysis patients | 250 mg following each dialysis during 7 days |
| Herpes zoster in immunocompromised adults | | |
| 500 mg three times daily for 10 days | ≥60 | 500 mg three times daily for 10 days |
| | 40 to 59 | 500 mg twice daily for 10 days |
| | 20 to 39 | 500 mg once daily for 10 days |
| | <20 | 250 mg once daily for 10 days |

| | | |
|--|------------------------|---|
| | Haemodialysis patients | 250 mg following each dialysis during 10 days |
| Genital herpes in immunocompetent adults – first episode of genital herpes | | |
| 250 mg three times daily for 5 days | ≥40 | 250 mg three times daily for 5 days |
| | 20 to 39 | 250 mg twice daily for 5 days |
| | <20 | 250 mg once daily for 5 days |
| | Haemodialysis patients | 250 mg following each dialysis during 5 days |
| Genital herpes in immunocompetent adults – episodic treatment of recurrent genital herpes | | |
| 125 mg twice daily for 5 days | ≥20 | 125 mg twice daily for 5 days |
| | <20 | 125 mg once daily for 5 days |
| | Haemodialysis patients | 125 mg following each dialysis during 5 days |
| Genital herpes in immunocompromised adults – episodic treatment of recurrent genital herpes | | |
| 500 mg twice daily for 7 days | ≥40 | 500 mg twice daily for 7 days |
| | 20 to 39 | 500 mg once daily for 7 days |
| | <20 | 250 mg once daily for 7 days |
| | Haemodialysis patients | 250 mg following each |

| | | |
|--|------------------------|--------------------------------|
| | | dialysis during 7 days |
| Suppression of recurrent genital herpes in immunocompetent adults | | |
| 250 mg twice daily | ≥40 | 250 mg twice daily |
| | 20 to 39 | 125 mg twice daily |
| | <20 | 125 mg once daily |
| | Haemodialysis patients | 125 mg following each dialysis |
| Suppression of recurrent genital herpes in immunocompromised adults | | |
| 500 mg twice daily | ≥40 | 500 mg twice daily |
| | 20 to 39 | 500 mg once daily |
| | <20 | 250 mg once daily |
| | Haemodialysis patients | 250 mg following each dialysis |

Patients with renal impairment on haemodialysis

Since 4-h haemodialysis resulted in up to 75% reduction in plasma penciclovir concentrations, famciclovir should be administered immediately following dialysis. The recommended dose regimens for haemodialysis patients are included in Table 1.

Patients with hepatic impairment

No dose adjustment is required in patients with mild or moderate hepatic impairment. No data are available for patients with severe hepatic impairment (see sections 4.4 and 5.2).

Elderly (≥65 years)

Dose modification is not required unless renal function is impaired.

Paediatric population

The safety and efficacy of famciclovir in children and adolescents aged less than 18 years have not been established. Currently available data are described in sections 5.1 and 5.2.

Method of administration

Famciclovir can be taken without regard to meals (see section 5.2).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Hypersensitivity to penciclovir.

4.4 Special warnings and precautions for use

Use in patients with renal impairment

In patients with impaired renal function dose adjustment is necessary (see sections 4.2 and 4.9).

Use in patients with hepatic impairment

Famciclovir has not been studied in patients with severe hepatic impairment. Conversion of famciclovir to its active metabolite penciclovir may be impaired in these patients resulting in lower penciclovir plasma concentrations, and thus a decrease of efficacy of famciclovir may occur.

Use for zoster treatment

Clinical response should be closely monitored, particularly in immunocompromised patients.

Consideration should be given to intravenous antiviral therapy when response to oral therapy is considered insufficient.

Patients with complicated herpes zoster, *i.e.* those with visceral involvement, disseminated zoster, motor neuropathies, encephalitis and cerebrovascular complications should be treated with intravenous antiviral therapy.

Moreover, immunocompromised patients with ophthalmic zoster or those with a high risk for disease dissemination and visceral organ involvement should be treated with intravenous antiviral therapy.

Transmission of genital herpes

Patients should be advised to avoid intercourse when symptoms are present even if treatment with an antiviral has been initiated. During suppressive treatment with antiviral agents, the frequency of viral shedding is significantly reduced. However, transmission is still possible. Therefore, in addition to therapy with famciclovir, it is recommended that patients use safer sex practices.

Excipient

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per film-coated tablet, that is to say essentially "sodium-free".

4.5 Interaction with other medicinal products and other forms of interactions

Effects of other medicinal products on famciclovir

No clinically significant interactions have been identified.

Concurrent use of probenecid may result in increased plasma concentrations of penciclovir, the active metabolite of famciclovir, by competing for elimination. Therefore patients receiving famciclovir at a dose of 500 mg three times daily co-administered with probenecid, should be monitored for toxicity. If patients experience severe dizziness, somnolence, confusion or other central nervous system disturbances, a dose reduction of famciclovir to 250 mg three times daily may be considered.

Famciclovir needs aldehyde oxidase to be converted into penciclovir, its active metabolite. Raloxifene has been shown to be a potent inhibitor of this enzyme *in vitro*. Co-administration of raloxifene could affect the formation of penciclovir and thus the efficacy of famciclovir. When raloxifene is co-administered with famciclovir the clinical efficacy of the antiviral therapy should be monitored.

4.6 Fertility, pregnancy and lactation

Women of child-bearing potential

There are no data supporting any special recommendations in women of child-bearing potential.

Patients with genital herpes should be advised to avoid intercourse when symptoms are present even if treatment has been initiated. It is recommended that patients use safer sex practice (see section 4.4).

Pregnancy

There is a limited amount of data (less than 300 pregnancy outcomes) from the use of famciclovir in pregnant women. Based on these limited amounts of information, the cumulative analysis of both prospective and retrospective pregnancy cases did not provide evidence indicating that the product causes any specific foetal defect or congenital anomaly. Animal studies have not shown any embryotoxic or teratogenic effects with famciclovir or penciclovir (the active metabolite of famciclovir). Famciclovir should only be used during pregnancy when the potential benefits of treatment outweigh the potential risks.

Breast-feeding

It is unknown whether famciclovir is excreted in human breast milk. Animal studies have shown excretion of penciclovir in breast milk. If the woman's condition mandates treatment with famciclovir, discontinuation of breast-feeding may be considered.

Fertility

Clinical data do not indicate an impact of famciclovir on male fertility following long-term treatment at an oral dose of 250 mg twice daily (see section 5.3).

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, patients who experience dizziness, somnolence, confusion or other central nervous system disturbances while taking famciclovir should refrain from driving or operating machinery.

4.8 Undesirable effects

Headache and nausea have been reported in clinical studies. These were generally mild or moderate in nature and occurred at a similar incidence in patients receiving placebo treatment. All other adverse reactions were added during post-marketing.

The pooled global placebo or active controlled clinical trials (n=2,326 for famciclovir arm) were retrospectively reviewed to obtain a frequency category for all adverse reactions mentioned below. The following table specifies the estimated frequency of adverse reactions based on all the spontaneous reports and literature cases that have been reported for famciclovir since its introduction to the market.

Adverse reactions (Table 2) are ranked under headings of frequency, using the following convention: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$), not known (cannot be estimated from available data).

Table 2: Adverse reactions from clinical trials and post-marketing spontaneous reports

Blood and lymphatic system disorders

Rare: thrombocytopenia

Psychiatric disorders

Uncommon: confusional state (predominantly in the elderly)

Rare: hallucinations

Nervous system disorders

Very common: headache

Common: dizziness

Uncommon: somnolence (predominantly in the elderly)

Not known: seizure*

Cardiac disorders

Rare: palpitations

Gastrointestinal disorders

Common: nausea, vomiting, abdominal pain, diarrhoea

Hepatobiliary disorders

Common: abnormal liver function tests

Rare: cholestatic jaundice

Immune system disorders

Not known: anaphylactic shock*, anaphylactic reaction*

Skin and subcutaneous tissue disorders

Common: rash, pruritus

Uncommon: angioedema (e.g. face oedema, eyelid oedema, periorbital oedema, pharyngeal oedema), urticaria

Not known: serious skin reactions* (e.g. erythema multiforme, Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis), hypersensitivity vasculitis*.

*Adverse drug reactions reported from post-marketing experience with famciclovir via spontaneous case reports and literature cases which have not been reported in clinical trials. Because these adverse drug reactions have been reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency.

Frequency is therefore listed as "not known".

Overall, adverse reactions reported from clinical studies with immunocompromised patients were similar to those reported in the immunocompetent population. Nausea, vomiting and abnormal liver function tests were reported more frequently, especially at higher doses.

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. Healthcare professionals are asked to report any suspected adverse reactions via HPRC Pharmacovigilance Website: www.hpra.ie

4.9 Overdose

Overdose experience with famciclovir is limited. In the event of an overdose supportive and symptomatic therapy should be given as appropriate. Acute renal failure has been reported rarely in patients with underlying renal disease where the famciclovir dose has not been appropriately reduced for the level of renal function. Penciclovir is dialysable; plasma concentrations are reduced by approximately 75% following 4 hours of haemodialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Nucleosides and nucleotides excluding reverse transcriptase inhibitors

ATC code: J05A B09

Mechanism of action

Famciclovir is the oral prodrug of penciclovir. Famciclovir is rapidly converted *in vivo* into penciclovir, which has *in vitro* activity against herpes simplex viruses (HSV types 1 and 2), varicella zoster virus (VZV), Epstein-Barr virus and cytomegalovirus.

The antiviral effect of orally administered famciclovir has been demonstrated in several animal models: this effect is due to *in vivo* conversion to penciclovir. In virus-infected cells the viral thymidine kinase (TK) phosphorylates penciclovir to a monophosphate form that, in turn, is converted to penciclovir triphosphate by cellular kinases. This triphosphate inhibits viral DNA chain elongation by competitive inhibition with deoxyguanosine triphosphate for incorporation into the growing viral DNA, thus halting virus replication of viral DNA. Penciclovir triphosphate has an intracellular half-life of 10 hours in HSV-1-, 20 hours in HSV-2- and 7 hours in VZV-infected cells grown in culture. In uninfected cells treated with penciclovir, concentrations of penciclovir triphosphate are only barely detectable. Hence the probability of toxicity to mammalian host cells is low and uninfected cells are unlikely to be affected by therapeutic concentrations of penciclovir.

Resistance

Like aciclovir, penciclovir resistance is associated with mutations principally in the thymidine kinase (TK) gene resulting in deficiency or altered substrate specificity of this enzyme. and to a much lesser extent in the DNA polymerase gene. Most aciclovir-resistant HSV and VZV clinical isolates are also resistant to penciclovir, but cross-resistance is not universal.

Results from 11 worldwide clinical studies involving penciclovir (topical or intravenous formulations) or famciclovir in immunocompetent or immunocompromised patients, including studies of up to 12 months treatment with famciclovir, have shown a small overall frequency of penciclovir resistant isolates: 0.2% (2/913) in immunocompetent patients and 2.1% (6/288) in immunocompromised patients. The resistant isolates were mostly found at the start of treatment or in a placebo group, with resistance occurring on or after treatment with famciclovir or penciclovir only in two immunocompromised patients.

Clinical efficacy

In placebo-controlled and active-controlled studies both in immunocompetent and immunocompromised patients with uncomplicated herpes zoster, famciclovir was effective in the resolution of lesions. In an active-controlled clinical study, famciclovir was shown to be effective in the treatment of ophthalmic zoster in immunocompetent patients.

Efficacy of famciclovir in immunocompetent patients with first episode of genital herpes was shown in three active-controlled studies. Two placebo-controlled studies in immunocompetent patients and one active-controlled study in HIV-infected patients with recurrent genital herpes showed that famciclovir was effective.

Two placebo-controlled 12-month studies in immunocompetent patients with recurrent genital herpes showed that famciclovir-treated patients had a significant reduction of recurrences as compared to placebo-treated patients. Placebo-controlled and uncontrolled studies of up to 16 weeks duration showed that famciclovir was effective in the suppression of recurrent genital herpes in HIV-infected patients; the placebo-controlled study showed that famciclovir significantly decreased the proportion of days of both symptomatic and asymptomatic HSV shedding.

Paediatric population

Famciclovir experimental oral granules were evaluated in 169 paediatric patients 1 month to ≤ 12 years of age. One hundred of these patients were 1 to ≤ 12 years of age and were treated with famciclovir oral granules (doses ranged from 150 mg to 500 mg) either twice (47 patients with herpes simplex virus infections) or three times (53 patients with chickenpox) daily for 7 days. The remaining 69 patients (18 patients 1 to ≤ 12 months, 51 patients 1 to ≤ 12 years) participated in single-dose pharmacokinetic and safety studies using famciclovir oral granules (doses ranged from 25 mg to 500 mg). Famciclovir weight-based doses were selected to provide penciclovir systemic exposures similar to the penciclovir systemic exposures observed in adults after administration of 500 mg famciclovir. None of these studies comprised a control group; therefore a conclusion on the efficacy of the investigated regimens is not possible. The safety profile was similar to that seen in adults. However, systemic drug exposure in infants < 6 months of age was low, thus precluding any assessment of famciclovir's safety in this age group.

5.2 Pharmacokinetic properties

General characteristics

Absorption

Famciclovir is the oral prodrug of the antivirally active compound penciclovir. Following oral administration, famciclovir is rapidly and extensively absorbed and converted to penciclovir. Bioavailability of penciclovir after oral administration of famciclovir was 77%. Mean peak plasma concentration of penciclovir, following a 125 mg, 250 mg, 500 mg and 750 mg oral dose of famciclovir, was 0.8 microgram/ml, 1.6 micrograms/ml, 3.3 micrograms/ml and 5.1 micrograms/ml, respectively, and occurred at a median time of 45 minutes post-dose.

Plasma concentration-time curves of penciclovir are similar following single and repeat (t.i.d. and b.i.d.) dosing, indicating that there is no accumulation of penciclovir on repeated dosing with famciclovir.

The extent of systemic availability (AUC) of penciclovir from oral famciclovir is unaffected by food.

Distribution

Penciclovir and its 6-deoxy precursor are poorly ($< 20\%$) bound to plasma proteins.

Biotransformation and elimination

Famciclovir is eliminated principally as penciclovir and its 6-deoxy precursor, which are excreted in urine. No unchanged famciclovir has been detected in urine. Tubular secretion contributes to the renal elimination of penciclovir.

The terminal plasma half-life of penciclovir after both single and repeat dosing with famciclovir was approximately 2 hours.

Evidence from preclinical studies has shown no potential for induction of cytochrome P450 enzymes and inhibition of CYP3A4.

Characteristics in special populations

Patients with herpes zoster infection

Uncomplicated herpes zoster infection does not significantly alter the pharmacokinetics of penciclovir measured after the oral administration of famciclovir. The terminal plasma half-life of penciclovir in patients with herpes zoster was 2.8 h and 2.7 h, respectively, after single and repeated dosing of famciclovir.

Subjects with renal impairment

The apparent plasma clearance, renal clearance, and plasma elimination rate constant of penciclovir decreased linearly with reductions in renal function, both after single and repeated dosing. Dose adjustment is necessary in patients with renal impairment (see section 4.2).

Subjects with hepatic impairment

Mild and moderate hepatic impairment had no effect on the extent of systemic availability of penciclovir following oral administration of famciclovir. No dose adjustment is recommended for patients with mild and moderate hepatic impairment (see sections 4.2 and 4.4). The pharmacokinetics of penciclovir have not been evaluated in patients with severe hepatic impairment. Conversion of famciclovir to the active metabolite penciclovir may be impaired in these patients resulting in lower penciclovir plasma concentrations, and thus possibly a decrease of efficacy of famciclovir.

Paediatric population

Repeated oral dosing of famciclovir (250 or 500 mg three times daily) to paediatric patients (6-11 years) infected with hepatitis B did not have notable effect on the pharmacokinetics of penciclovir compared to single dose data. There was no accumulation of penciclovir. In children (1-12 years) with herpes simplex virus infection or chickenpox given single oral doses of famciclovir (see section 5.1), the apparent clearance of penciclovir increased with body weight in a nonlinear manner. The plasma elimination half-life of penciclovir tended to decrease with decreasing age, from an average of 1.6 hours in the patients aged 6-12 years to 1.2 hours in patients aged 1-<2 years.

Elderly (≥65 years)

Based on cross-study comparisons, the mean penciclovir AUC was about 30% higher and penciclovir renal clearance about 20% lower after oral administration of famciclovir in elderly volunteers (65-79 years) compared to younger volunteers. Partly this difference may be due to differences in renal function between the two age groups. No dose adjustment based on age is recommended unless renal function is impaired (see section 4.2).

Gender

Small differences in renal clearance of penciclovir between females and males have been reported and were attributed to gender differences in renal function. No dose adjustment based on gender is recommended.

5.3 Preclinical safety data

General toxicity

Studies on safety pharmacology and repeated-dose toxicity reveal no special hazard for humans.

Genotoxicity

Famciclovir was not found to be genotoxic in a comprehensive battery of *in vivo* and *in vitro* tests designed to detect gene mutation, chromosomal damage and repairable damage to DNA. Penciclovir, in common with other substances of this class, has been shown to cause mutations/chromosomal aberrations in human lymphocytes and in the L5178Y mouse lymphoma assay at concentrations at least 25-fold to 100-fold, respectively higher than the maximum concentration reached in human plasma after a single oral famciclovir dose of 1500 mg. Penciclovir was negative in the bacterial Ames test and there was no evidence of increased DNA repair *in vitro*.

Penciclovir caused an increased incidence of micronuclei in mouse bone marrow *in vivo* when administered intravenously at doses highly toxic to bone marrow (≥ 500 mg/kg corresponding to ≥ 810 times the maximum human dose based on body surface area conversion).

Carcinogenicity

At high doses in female rats, there was an increased incidence of mammary adenocarcinoma, a tumour commonly observed in the strain of rats used in the carcinogenicity study. There was no effect on the incidence of neoplasia in male rats treated at doses up to 240 mg/kg/day (corresponding to a 38.4 mg/kg human equivalent dose or 1.3-fold of the highest recommended total daily dose of 1500 mg famciclovir or a patient of 50 kg body weight) or in mice of either sex at doses up to 600 mg/kg/day (corresponding to a 48 mg/kg human equivalent dose or 1.6-fold of the highest recommended total daily dose).

Reproductive toxicity

Impaired fertility (including histopathological changes in the testis, altered sperm morphology, reduced sperm concentration and motility, and reduced fertility) was observed in male rats after 10 weeks of dosing at 500 mg/kg/day (corresponding to a 80 mg/kg human equivalent dose or 2.7-fold of the highest recommended total daily dose).

Furthermore, testicular toxicity was noted in the general toxicity studies. This finding was reversible and has also been observed with other substances of this class. Animal studies did not indicate any negative effect on female fertility at doses up to 1,000 mg/kg/day (corresponding to a 160 mg/kg human equivalent dose or 5.3-fold of the highest recommended total daily dose).

Embryofoetal development studies showed no evidence of adverse effects at oral doses of famciclovir and intravenous doses of penciclovir corresponding to 0.7- to 5.3-fold of the highest recommended total daily dose of famciclovir.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core

Microcrystalline cellulose E460
Colloidal anhydrous silica E551
Sodium starch glycolate (Type A)
Low-substituted hydroxypropylcellulose
Croscarmellose sodium
Sodium stearyl fumarate

Film-coat

Titanium dioxide E 171
Polydextrose E1200
Hypromellose E464
Triacetin E1518
Macrogol 8000

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Keep the blister in the outer carton in order to protect from light.

6.5 Nature and contents of container

White opaque PVC/PE/Aclar – Aluminium blisters packs

1, 12, 14, 15, 20, 21, 30, 56 & 60 film-coated tablets. Hospital packs of 50 (50 x 1) film-coated tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Teva Pharma B.V.
Swansweg 5
2031GA Haarlem
Netherlands

8 MARKETING AUTHORISATION NUMBER

PA0749/025/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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