
Name of Medicine

Fluanxol[®] Depot

Flupenthixol decanoate Injection 20 mg/mL

Fluanxol[®] Concentrated Depot

Flupenthixol decanoate Injection 100 mg/mL

Presentation

Flupenthixol decanoate is insoluble in water, soluble in alcohol, ether and chloroform.

Fluanxol Depot injection presents as a clear, colourless to slightly yellowish oil.

Fluanxol Concentrated Depot injection presents as a clear, yellowish to yellow oil.

Uses

Actions

Flupenthixol is a potent, relatively non sedating, neuroleptic drug of the thioxanthene class. In low to moderate dosages (up to 100 mg/2 weeks) Fluanxol is non-sedating, while a sedative effect may be expected when higher doses are administered. Flupenthixol shows antipsychotic effects in patients with schizophrenia. It may be of benefit in patients with flat or depressed affect. In low doses, Fluanxol possesses disinhibiting and mood elevating properties.

Flupenthixol dose-dependently increases the serum prolactin levels.

Pharmacokinetics

The decanoic acid esterification of flupenthixol results in the slow release of the drug from the oily solution at the injection site with consequent prolongation of duration of action. The onset of action usually occurs in the range of 24 to 72 hours after injection and the improvement of symptoms continues for 2 to 4 weeks. A pre-injection serum concentration of 2 - 8 nmol/L is recommended for maintenance treatment of schizophrenic patients with a low - moderate degree of illness. However, there is considerable variation in the individual response of patients to flupenthixol decanoate and its use for maintenance therapy requires careful supervision. The maximal serum concentration is reached at the end of the first week after injection. Estimates of half-life varied considerably between studies; elimination is prolonged, in the order of 3 weeks to 3 months and probably reflects release of the active compound from the depot.

Steady state is probably achieved within 3 to 6 months. The depot is administered every 2 to 4 weeks. Limited data suggest that excretion and metabolism proceeds along the same routes as found in animals. In one human study urine contained flupenthixol, N-dealkyl flupenthixol and their corresponding sulphoxides. After an oral dose another study demonstrated a relatively small amount of flupenthixol in urine and faeces.

Indications

Fluanxol Depot injection

Fluanxol injection is a depot neuroleptic preparation and is indicated in the treatment and maintenance of schizophrenic patients, especially those who are unreliable in taking the medicine prescribed for them.

Fluanxol Concentrated Depot injection

Fluanxol Concentrated injection is a depot neuroleptic preparation and is indicated in the treatment of moderate to severe schizophrenia and allied psychoses. Patients for whom the drug is especially appropriate are:

1. Those believed by the physician to be unreliable in taking oral medication.
2. Patients who are already receiving treatment with Fluanxol injection at high dose levels and who may experience discomfort as a result of the large injection volume.
3. Patients who hitherto could not receive effective treatment with depot neuroleptics because of the high doses, and hence large volumes, required to achieve satisfactory therapeutic blood levels.

Features of the illness most likely to benefit are hallucinations, paranoid delusions, apathy, inertia, withdrawal and anxiety.

Dosage and Administration

Adults

Fluanxol (flupenthixol decanoate) is administered by intramuscular injection, in the gluteus maximus. Fluanxol is NOT for intravenous use. It is not intended for short-term therapy (less than 3 months).

As a long-acting depot preparation, Fluanxol has been found useful in the maintenance treatment of non-agitated chronic schizophrenic patients who have been stabilised with short-acting neuroleptics and might benefit from transfer to a longer-acting injectable medication. The changeover of medication should aim at maintaining a clinical outcome similar to or better than that obtained with the previous therapy. To achieve and maintain the optimum dose, the changeover from other neuroleptic medication should proceed gradually and constant supervision is required during the period of dosage adjustment in order to minimise the risk of overdose or insufficient suppression of psychotic symptoms before the next injection.

Patients not previously treated with long-acting depot neuroleptics should be given an initial test dose of 5 mg to 20 mg. An initial dose of 20 mg is usually well tolerated: however, a 5 mg test dose is recommended in elderly, frail and cachectic patients, and in patients whose individual or family history suggests a predisposition to extrapyramidal reactions. In the subsequent 5 to 10 days, the therapeutic response and the appearance of extrapyramidal symptoms should be carefully monitored. Oral neuroleptic drugs may be continued, but in diminishing dosage, during this period.

In patients previously treated with long-acting depot neuroleptics who displayed good tolerance to these drugs, an initial dose of 20 to 40 mg may be adequate. Patients transferred from fluphenazine decanoate should receive flupenthixol decanoate in a dose ratio of 25 mg fluphenazine decanoate equals 40 mg flupenthixol decanoate. For haloperidol decanoate, dose equivalence has not been systematically established, but is approximately 40 mg flupenthixol decanoate equals 50 mg haloperidol decanoate.

Subsequent doses and the frequency of administration must be determined for each patient. There is no reliable dosage comparability between a shorter-acting neuroleptic and depot flupenthixol, and therefore, the dosage of the long-acting drug must be individualised.

Except in particularly sensitive patients, a second dose of 20 mg or 40 mg can be given 4 to 10 days after the initial injection. Subsequent dosage adjustments are made in accordance with the response of the patient, but the majority of patients can be adequately controlled by 20 to 40 mg of Fluanxol every 2 to 4 weeks. The optimal amount of the drug has been found to vary with the clinical circumstances and individual response.

Since higher doses increase the incidence of extrapyramidal reactions and other adverse effects, the amount of drug used should not be increased merely in order to prolong the intervals between injections. With higher doses there may also be more variability in the action of Fluanxol and, therefore, unit dose increments should not exceed 20 mg (1.0 mL). If volumes larger than 2 - 3 mL of the 20 mg/mL solution are required, the 100 mg/mL should be preferred. After an appropriate dosage adjustment is achieved, regular and continuous supervision and reassessment is considered essential in order to permit any further dosage adjustments that might be required to ensure use of the lowest effective individual dose and avoid troublesome side effects.

Fluanxol Concentrated Depot

Doses greater than 100 mg/fortnight are usually not deemed necessary although higher doses have been used occasionally in some treatment-resistant patients.

Patients who require higher doses of Fluanxol Depot to control symptoms of schizophrenia and/or those who complain of discomfort with a large injection volume may be administered Fluanxol Concentrated Depot (100 mg/mL) in preference to Fluanxol Depot (20 mg/mL).

AS WITH ALL OILY INJECTIONS IT IS IMPORTANT TO ENSURE, BY ASPIRATION BEFORE INJECTION, THAT INADVERTENT INTRAVASCULAR INJECTION DOES NOT OCCUR.

Contraindications

Flupenthixol is contraindicated in patients with known hypersensitivity to the thioxanthenes. The possibility of cross sensitivity between the thioxanthenes and phenothiazine derivatives should be considered.

Flupenthixol is also contraindicated in patients with known hypersensitivity to the excipient used (coconut oil - fractionated) in the injection.

Flupenthixol is also contraindicated in the presence of depressed level of consciousness due to any cause (e.g. intoxication with alcohol, barbiturates or opiates), circulatory collapse, coma, suspected or established subcortical brain damage, blood dyscrasias and phaeochromocytoma.

Flupenthixol is not recommended for use in children (see **Warnings and Precautions**).

Warnings and Precautions

Neuroleptic Malignant Syndrome - The neuroleptic malignant syndrome (NMS) is a rare but potentially fatal complication of the use of neuroleptic drugs. Core features of NMS are hyperthermia, muscle rigidity and fluctuating consciousness along with autonomic dysfunction (labile blood pressure, tachycardia, diaphoresis). Aside from immediate cessation of the neuroleptic medication the use of general supportive measures and symptomatic treatment are vital. Note that neuroleptic malignant syndrome has been reported with Fluanxol.

Initiation of therapy - Severe adverse reactions requiring immediate medical attention may occur and are difficult to predict. Therefore, the evaluation of tolerance and response, and

establishment of adequate maintenance therapy require careful stabilisation of each patient under continuous, close medical observation and supervision.

Special patient groups - Fluanxol should be used with caution in liver damage, cerebrovascular or renal insufficiency, and severe cardiovascular disorders. It is not indicated for the management of severely agitated psychotic patients, psychoneurotic patients or geriatric patients with confusion and/or agitation, as these characteristics may be exaggerated.

Reduced hepatic function - Significant reduction of liver function may cause a decrease in the elimination rate of Fluanxol. Careful dosing and, if possible, a serum level determination is advisable in patients with reduced liver function (see also **Pharmacokinetics**).

Parkinsonism - The drug should be used with caution in patients with Parkinsonism.

Arteriosclerosis - The drug should be used with caution in patients with severe arteriosclerosis.

Cellular depression - If any soreness of the mouth, gums or throat or any symptoms of upper respiratory infection occur and confirmation leukocyte count indicates cellular depression, therapy should be discontinued and other appropriate measures instituted immediately.

Organic brain syndrome - Like other neuroleptics, Fluanxol should be used with caution in patients with organic brain syndrome.

Stroke - An approximate 3-fold increase in risk of cerebrovascular adverse events has been seen in randomised placebo-controlled clinical trials in the dementia population with some *atypical* antipsychotics. The mechanism for this increased risk is not known. An increased risk cannot be excluded for other antipsychotics or other patient populations. Therefore, flupenthixol decanoate should be used with caution in patients with risk factors for stroke.

Convulsions - Flupenthixol should be used with caution in patients with a history of convulsions since it may lower the convulsive threshold.

Anticholinergic effects - Although its anticholinergic properties are weak, flupenthixol should be used with caution in patients who are known or are suspected to have glaucoma, and in those patients who might be exposed to extreme heat, or organophosphorus insecticides or who are receiving atropine or related drugs. Paralytic ileus has occasionally been reported, particularly in the elderly, when several drugs with anticholinergic effects have been used simultaneously.

Laboratory tests required - Blood dyscrasias and liver damage have been reported sporadically with this class of drugs including Fluanxol. Therefore, routine blood counts and hepatic function tests are advisable, particularly during the first months of therapy. Should either of these disorders occur, supportive treatment should be instituted and further injections avoided.

Cardiac disorders - Caution should be observed when using a drug of this category in patients who may have a propensity for development of defects in cardiac conduction.

As with other drugs belonging to the therapeutic class of antipsychotics, flupenthixol decanoate may cause QT prolongation. Persistently prolonged QT intervals may increase the risk of malignant arrhythmias. Therefore, flupenthixol decanoate should be used with caution in susceptible individuals (with hypokalaemia, hypomagnesaemia or genetic predisposition) and in patients with a history of cardiovascular disorders, e.g. QT prolongation, significant bradycardia (< 50 beats per minute), recent acute myocardial infarction, uncompensated heart failure, or cardiac arrhythmia. Concomitant treatment with other antipsychotics should be avoided (see **Interactions**).

Venous thromboembolism (VTE) – cases have been reported with antipsychotic drugs. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with flupenthixol decanoate and preventive measures undertaken.

Increased Mortality in Elderly people with Dementia

Data from two large observational studies showed that elderly people with dementia who are treated with antipsychotics are at a small increased risk of death compared with those who are not treated. There are insufficient data to give a firm estimate of the precise magnitude of the risk and the cause of the increased risk is not known.

Diabetes - As described for other psychotropics, flupenthixol decanoate may modify insulin and glucose responses calling for adjustment of the antidiabetic therapy in diabetic patients.

Surgery - Patients on large doses of flupenthixol who are undergoing surgery should be watched carefully for possible hypotensive phenomena, and dosages of anaesthetic or central nervous system depressant agents may have to be reduced.

Monitoring - Patients on long term therapy, particularly on high doses, should be evaluated periodically to decide whether the maintenance dosage can be lowered or drug therapy discontinued.

Persistent tardive dyskinesia - Tardive dyskinesia may develop in some patients on long-term therapy with antipsychotic medications or may occur after therapy has been discontinued. The risk seems to be greater in elderly patients on high dose therapy, especially females. The symptoms are potentially irreversible in some patients. The syndrome is characterised by rhythmical involuntary movements of the tongue, face, mouth or jaw. Sometimes these may be accompanied by involuntary movements of the extremities. There is no known effective treatment available for tardive dyskinesia; antiparkinson agents usually do not alleviate the symptoms. It is suggested that all antipsychotic agents be gradually reduced and withdrawn, if possible, if these symptoms appear. It has been reported that fine vermicular movements of the tongue may be the first sign of the syndrome and if medication is stopped at this time the syndrome may remit. If it is necessary to reinstitute treatment or increase the dosage or change to a different antipsychotic agent, the syndrome may be masked.

Antiemetic effect - The antiemetic effect observed with flupenthixol in animal studies may also occur in man; therefore, the drug may mask signs of toxicity due to overdosage of other drugs, or it may mask the symptoms of disease, such as brain tumor or intestinal obstruction.

Effect on laboratory tests - Transient slight alterations in liver function tests have infrequently been reported.

Paediatric use - Since the safety and efficacy of flupenthixol in children have not been established, its use is not recommended in the paediatric age group (see **Contraindications**).

Safety Experience in Elderly Patients with Dementia-related Psychosis

In elderly patients with dementia-related psychosis, the efficacy of flupenthixol has not been established. Observational studies suggest that elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Risk factors that may predispose this patient population to increased risk of death when treated with antipsychotics include age >80 years, sedation, concomitant use of benzodiazepines, or presence of pulmonary conditions (e.g. pneumonia, with or without aspiration).

Pregnancy and Lactation

Category C

Safety in pregnancy has not been established. Therefore it should not be administered to women of childbearing potential unless, in the opinion of the physician, the expected benefit to the patient outweighs the potential risk to the foetus.

Non teratogenic class effect:

Neonates exposed to antipsychotic drugs (including flupenthixol) during the third trimester of pregnancy are at risk of experiencing extrapyramidal neurological disturbances and/or withdrawal symptoms following delivery. There have been post-market reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder in these neonates. These complications have varied in severity; while in some cases symptoms have been self-limited; in other cases neonates have required additional medical treatment or monitoring.

Flupenthixol should be used during pregnancy only if the anticipated benefit outweighs the risk and administered dose and duration of treatments should be as low and short as possible.

Small amounts of the drug are excreted in breast milk so that lactating mothers should undertake alternative feeding of the infant.

Effects on ability to drive and use machines

Although flupenthixol is a relatively non-sedating drug, sedation may occur in some patients. Therefore, ambulatory patients should be warned about engaging in activities such as driving a car or operating machinery.

Other

Nil

Adverse Effects

The most common adverse reaction reported with flupenthixol has been extrapyramidal disorder.

Flupenthixol shares many of the pharmacological properties of other thioxanthenes and phenothiazines. Therefore, the known adverse reactions of these drugs should be borne in mind when flupenthixol is used.

Central Nervous System

Extrapyramidal symptoms, including hypo- and hyperkinetic states, tremors, pseudoparkinsonism, dystonia, hypertonia, akathisia, oculogyric crises and tardive dyskinesia (see **Warnings and Precautions**). The symptoms, if they are to occur, usually appear within the first few days after administration and can usually be controlled or totally curtailed by reduction in dosage and/or standard antiparkinsonian medication. The incidence of extrapyramidal symptoms appears to be more frequent with the first few injections of flupenthixol, and diminish thereafter. The routine prophylactic use of antiparkinsonian medication is not recommended. Extrapyramidal reactions may be alarming, and patients should be forewarned and reassured.

Other CNS effects reported with flupenthixol include restlessness, insomnia, overactivity, psychomotor agitation, involuntary muscle contractions, tics, hypomania, epileptiform convulsions, headache, drowsiness, somnolence, depression, fatigue, and anergia.

Neuroleptic malignant syndrome has been reported with Fluanxol (see **Warnings and Precautions**).

Autonomic Nervous System

Dry mouth, blurred vision, constipation, excessive salivation, excessive perspiration, nausea, disturbances in micturition, dizziness, palpitations and fainting have been observed with flupenthixol but are uncommon. Miosis, mydriasis, paralytic ileus, polyuria, nasal congestion, glaucoma, tachycardia, hypotension, hypertension, fluctuations in blood pressure, non-specific ECG changes and cardiac arrhythmias have been reported with related drugs. If hypotension occurs, adrenaline should not be used as a pressor agent since a paradoxical further lowering of blood pressure may result.

Metabolic and Endocrine

Weight changes, gynaecomastia, impotence, loss of libido, and sexual excitement have been reported with flupenthixol. Elevated serum prolactin levels may cause hormonal effects in some patients e.g. menstrual disturbance, galactorrhoea in men and women. Related drugs have been also associated with false positive pregnancy tests, peripheral oedema, gynaecomastia, hypo and hyperglycaemia and glycosuria. Elevated creatine phosphokinase levels have also been reported.

Pregnancy, puerperium and perinatal conditions

Neonatal drug withdrawal syndrome – frequency not known.

Toxic and Allergic

Isolated cases of hyperbilirubinaemia, jaundice, SLE and haemolytic-uraemic syndrome have been reported. Blood dyscrasias (leukopenia, agranulocytosis, pancytopenia, aplastic anaemia, thrombocytopenia and thrombocythaemia) have been reported with flupenthixol but the causality has not been confirmed.

Increased levels of AST, ALT and alkaline phosphatase have also been reported. Other antipsychotic drugs have been associated with leukopenia, agranulocytosis, thrombocytopenic or nonthrombocytopenic purpura, haemolytic anaemia and pancytopenia.

Skin reactions, such as rash, and erythema have rarely been reported with flupenthixol (frequency < 1 %). Alopecia and eczema have also been reported with flupenthixol. The possibility of anaphylactoid reactions occurring in some patients should be borne in mind.

Local Tolerance

Injection site reactions have been reported: local inflammation and abscess.

Ophthalmological

Lenticular and corneal opacities have been seen following long-term use of phenothiazines, but not reported with Fluanxol.

Gastrointestinal

Dysphagia, gingival hypertrophy, hepatitis and hepatic failure have been reported.

Cardiovascular

Cardiac failure has been reported. As with other drugs belonging to the therapeutic class of antipsychotics, rare cases of QT prolongation, ventricular arrhythmias - ventricular fibrillation, ventricular tachycardia, Torsade de Pointes and sudden unexplained death have been reported for flupenthixol decanoate (see **Warnings and Precautions**).

Vascular Disorders

Venous thromboembolism, very rare.

Discontinuation

Abrupt discontinuation of flupenthixol decanoate may be accompanied by withdrawal symptoms. The most common symptoms are nausea, vomiting, anorexia, diarrhoea, rhinorrhoea, sweating, myalgias, paraesthesias, insomnia, restlessness, anxiety, and agitation. Patients may also experience vertigo, alternate feelings of warmth and coldness, and tremor. Symptoms generally begin within 1 to 4 days of withdrawal and abate within 7 to 14 days.

Miscellaneous

Sudden, unexpected and unexplained deaths have occasionally been reported in patients who have received certain phenothiazine derivatives. Previous brain damage or seizures may be predisposing factors; high doses should be avoided in known seizure patients. Several patients have shown flare-ups of psychotic behaviour patterns shortly before death. Autopsy findings have usually revealed acute fulminating pneumonia or pneumonitis, aspiration of gastric contents or intramyocardial lesions.

Polymyositis and facial oedema have also been reported.

Interactions

Tricyclic antidepressants - Tricyclic antidepressants and neuroleptics mutually inhibit the metabolism of each other.

Lithium - Concomitant use of neuroleptics and lithium increases the risk of neurotoxicity.

MAO Inhibitors - Although no specific clinical incompatibilities have been encountered, on theoretical pharmacodynamic grounds, it may be wise to allow an interval of not less than 2 weeks between completion of MAOI treatment and the initiation of flupenthixol treatment.

Alcohol, other CNS depressant drugs - Fluanxol may enhance the sedative effects of alcohol and the effects of barbiturates and other CNS depressants (including opioid analgesics).

As with other neuroleptics, the plasma concentration of flupenthixol may be decreased by concomitant administration of phenobarbitone and carbamazepine and influenced by the intake of alcohol.

Hypnotics - As with all phenothiazines, Fluanxol should not be used concomitantly with large doses of hypnotics due to the possibility of potentiation.

Antihypertensives - Neuroleptics may increase or reduce the effect of antihypertensive drugs.

Fluanxol should not be given concomitantly with guanethidine, debrisoquine, clonidine or similarly acting compounds since neuroleptics may block the antihypertensive effect of these compounds.

Levodopa, adrenergic drugs - Fluanxol may lower the effect of levodopa and adrenergic drugs.

Metoclopramide, piperazine - Concomitant use of metoclopramide or piperazine increases the risk of extrapyramidal disorder.

Drugs known to increase the QT interval - Increases in the QT interval related to antipsychotic treatment may be exacerbated by the co-administration of other drugs known to significantly increase the QT interval. Co-administration of such drugs should be avoided. Relevant classes include:

- class Ia and III antiarrhythmics (e.g. quinidine, amiodarone, sotalol, dofetilide)
- some antipsychotics (e.g. thioridazine)
- some macrolides (e.g. erythromycin)
- some antihistamines (e.g. terfenadine, astemizole)
- some quinolone antibiotics (e.g. gatifloxacin, moxifloxacin)

The above list is not exhaustive and other individual drugs known to significantly increase the QT interval (e.g. cisapride, lithium) should be avoided.

Drugs known to cause electrolyte disturbances such as thiazide diuretics (hypokalaemia) and drugs known to increase the plasma concentration of flupenthixol decanoate should also be used with caution as they may increase the risk of QT prolongation and malignant arrhythmias (see **Warnings and Precautions**).

Overdosage

In general, the main therapy for all overdoses is supportive and symptomatic care.

Symptoms

Overdosage may cause somnolence, coma, extreme agitation, excitement, confusion, convulsions, extrapyramidal symptoms, shock, respiratory and circulatory collapse and hyperthermia/hypothermia.

ECG changes, QT prolongation, Torsade de Pointes, cardiac arrest and ventricular arrhythmias have been reported when administered in overdose together with drugs known to affect the heart.

Treatment

Treatment is symptomatic and supportive. No further injections of flupenthixol should be given. Measures to support the respiratory and cardiovascular systems should be instituted. If severe hypotension occurs, an i.v. vasopressor drug should be administered immediately. Epinephrine (adrenaline) should **not** be used as further lowering of blood pressure may result. Convulsions may be treated with diazepam and extrapyramidal symptoms with an antiparkinsonian medication.

For further advice on management of overdose please contact the Poisons Information Centre (Tel: 13 11 26 for Australia and Tel: 0800 764 766 for New Zealand).

Pharmaceutical Precautions

Instructions for Use/Handling

Nil

Incompatibilities

Flupenthixol decanoate should not be mixed with depot formulations that use sesame oil as the vehicle, because this would result in definite changes in the pharmacokinetic properties of the involved preparations.

Shelf Life

4 years

Special Precautions for Storage

Store below 25°C. Protect from light.

Medicine Classification

Prescription only medicine

Package Quantities

Fluanxol Depot

- Solution for injection containing 20 mg/mL flupenthixol decanoate.
- 1 mL (20 mg) and 2 mL (40 mg) glass ampoules in packs of 5 ampoules.

Fluanxol Concentrated Depot

- Concentrated injection containing 100 mg/mL flupenthixol decanoate.
- 1 mL (100 mg) glass ampoules in packs of 5 ampoules.

Further Information

Flupenthixol decanoate

Chemical name:

cis (z)-2-[4-[3-(2-(trifluoromethyl) thioxanthenylidene - (9)) propyl] - piperaziny - (1)] ethanol - (1) decanoic acid ester

CAS number:

30909-51-4

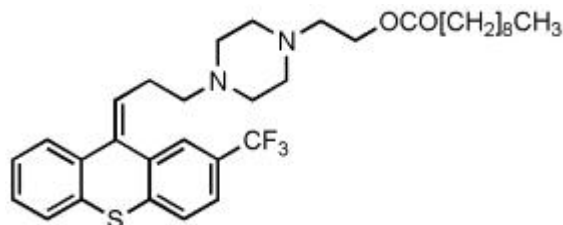
Molecular formula:

C₃₃H₄₃F₃N₂O₂S

Molecular weight:

588.82

Structural formula:



Excipients:

Fluanxol Depot and Fluanxol Concentrated Depot injections contain the following excipient:
coconut oil – fractionated.

Name and Address

Australian Sponsor:

Lundbeck Australia Pty Ltd
1 Innovation Rd
North Ryde NSW 2113
Ph: +61 2 8669 1000

New Zealand Sponsor:

Healthcare Logistics
PO Box 62027
Mt Wellington, Auckland
Ph: + 64 9 9185100

Date of Preparation

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