Megval™ 50 mg

Combi pack of Drug Product and Sterile Diluent - Melphalan Hydrochloride for Injection 50mg/vial and Sterile Diluent [for Solution for Injection/Infusion]

1 NAME OF THE MEDICINE

Megval 50 mg, Combi pack of drug product and sterile diluent.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each single-use vial contains melphalan hydrochloride equivalent to 50 mg melphalan.

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

3 PHARMACEUTICAL FORM

Megval for Injection is supplied as a sterile, non pyrogenic, freeze-dried powder.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Megval Injection is indicated for the treatment of patients with multiple myeloma for whom oral therapy is not appropriate.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage:

Megval for Injection is reconstituted using the sterile diluent provided

Megval for Injection is administered intravenously. The usual IV dose is 16 mg/m². The drug is administered as a single infusion over 15 to 20 minutes. Megval is administered at 2-week intervals for four doses, then, after adequate recovery from toxicity, at 4-week intervals. Available evidence suggests about one third to one half of the patients with multiple myeloma show a favourable response to the drug. Experience with oral melphalan suggests that repeated courses should be given since improvement may continue slowly over many months, and the maximum benefit may be missed if treatment is abandoned prematurely. Dose adjustment on the basis of blood cell counts at the nadir and day of treatment should be considered.

Patients with renal impairment

Melphalan clearance, though variable, is decreased in patients with renal impairment. Dosage reduction of up to 50% should be considered in patients with moderate to severe renal impairment and subsequent dosage determined according to the degree of haematological suppression.

Administration Precautions:

As with other toxic compounds, caution should be exercised in handling and preparing the solution of Megval. Appropriate guidelines for the handling of cytotoxic compounds should be consulted. Skin reactions associated with accidental exposure may occur. The use of disposable latex or PVC gloves, facemask, protective goggles and a disposable apron is recommended. If the solution of Megval contacts the skin or mucosa, immediately wash the skin or mucosa thoroughly with soap and cold water. In such instances it may be prudent to seek medical advice.

In case of contact with eyes, IMMEDIATE irrigation with sodium chloride eyewash should be carried out and medical attention sought without delay. If sodium chloride solution is not available, large volumes of water may be used.

Any spillage should be dealt with immediately (by personnel wearing suitable protective clothing), by mopping with damp, disposable paper towels which are placed in a high-risk waste disposal bag. Contaminated surfaces should be washed with copious quantities of water.

Preparation for Administration/Stability:

Preparation for Administration/Stability:

1. Megval for Injection must be reconstituted AT ROOM TEMPERATURE by rapidly injecting 10 mL of the supplied diluent directly into the vial of lyophilised powder using a sterile needle (20-gauge or larger needle diameter) and syringe. Immediately shake vial vigorously until a clear solution is obtained. This provides a 5 mg/mL solution of melphalan and has a pH of approximately 6.5. Rapid addition of the diluent, as a single quantity, followed by immediate vigorous shaking is important for proper dissolution.
2. Immediately dilute the dose to be administered in 0.9% Sodium Chloride Injection to a concentration not greater than 0.45 mg/mL.
3. Administer the diluted product over a minimum of 15 minutes.
4. Complete administration within 60 minutes of reconstitution. Parenteral drug products should be visually inspected for particulate matter and discolouration prior to administration whenever solution and container permit. If either occurs, do not use this product.

The time between reconstitution/dilution and administration of Megval should be kept to a minimum because reconstituted and diluted solutions of Megval are unstable. Over as short a time as 30 minutes, a citrate derivative of melphalan has been detected in reconstituted material from the reaction of Megval with Sterile Diluent for Megval Upon further dilution with saline, nearly 1% label strength of melphalan hydrolyses every 10 minutes.

A precipitate forms if the reconstituted solution is stored at 5°C. DO NOT REFRIGERATE THE RECONSTITUTED PRODUCT. Megval Injection contains no antimicrobial agent. It is for single use in one patient only. Any unused solution should be discarded (see 6.6 SPECIAL PRECAUTIONS FOR DISPOSAL).

4.3 CONTRAINDICATIONS

Megval should not be used in patients whose disease has demonstrated prior resistance to this agent. Patients who have demonstrated hypersensitivity to melphalan should not be given the drug.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Identified precautions

Melphalan hydrochloride should be administered in carefully adjusted dosage under the direction of physicians experienced in the use of cytotoxic agents.

Immunisation using a live organism vaccine has the potential to cause infection in immunocompromised hosts. Therefore, immunisations with live organism vaccines are not recommended.

Severe bone marrow suppression with resulting infection or bleeding may occur. Since melphalan hydrochloride is a potent myelosuppressive agent, it is essential that careful attention should be paid to the monitoring of blood counts to avoid the possibility of excessive myelosuppression and the risk of irreversible bone marrow aplasia. Therefore, the following tests should be performed at the start of therapy and prior to each subsequent dose of melphalan hydrochloride: platelet count, haemoglobin, white blood cell count, and differential. Thrombocytopenia and/or leucopoenia are indications to withhold further therapy until the blood counts have sufficiently recovered. Frequent blood counts are essential to determine optimal dosage and to avoid toxicity. Dose adjustment on the basis of blood counts at the nadir and day of treatment should be considered. See 4.2 DOSE AND METHOD OF ADMINISTRATION.

Blood counts may continue to fall after treatment is stopped, so at the first sign of an abnormally large fall in leucocyte or platelet counts, treatment should be temporarily interrupted. Controlled trials comparing intravenous (IV) to oral melphalan have shown more myelosuppression with the IV formulation. Melphalan hydrochloride should be used with extreme caution in patients whose bone marrow reserve may have been compromised by prior irradiation or chemotherapy or whose marrow function is recovering from previous cytotoxic therapy.

Hypersensitivity reactions including anaphylaxis have occurred in approximately 2% of patients who received the IV formulation. See 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS). These reactions usually occur after multiple courses of treatment. Treatment is symptomatic. The infusion should be terminated immediately, followed by the administration of volume expanders, pressor agents, corticosteroids, or antihistamines at the discretion of the physician. If a hypersensitivity reaction occurs, IV or oral melphalan should not be readministered since hypersensitivity reactions have also been reported with oral melphalan.

Melphalan hydrochloride may cause local tissue damage should extravasation occur, and consequently it should not be administered by direct injection into a peripheral vein.

In all instances where the use of melphalan hydrochloride Injection is considered for chemotherapy, the physician must evaluate the need and usefulness of the drug against the risk of adverse events.

Use in renal impairment

Melphalan clearance may be reduced in patients with renal impairment, who may also have uraemic bone marrow suppression. Dosage reduction may therefore be necessary (see 4.2 DOSE AND METHOD OF ADMINISTRATION), and these patients should be closely observed. In one trial, increased bone marrow suppression was observed in patients with BUN levels ≥30 mg/dL (≥10.71 mmol/L). A 50% reduction in the IV melphalan dose decreased the incidence of severe bone marrow suppression in the latter portion of this study.

Use in the elderly

Clinical experience with melphalan has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Paediatric use

Safety and efficacy in children have not been established.

Effects on laboratory tests

Periodic complete blood counts with differentials should be performed during the course of treatment with Megval. At least one determination should be obtained prior to each dose. Patients should be observed closely for consequences of bone marrow suppression, which include severe infections, bleeding, and symptomatic anaemia.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Cyclosporin:

Impaired renal function has been described in bone marrow transplant patients who were conditioned with high-dose intravenous melphalan and who subsequently received cyclosporin to prevent graft-versus-host disease.

Cisplatin/Carmustine:

Cisplatin may affect melphalan kinetics by inducing renal dysfunction and subsequently altering melphalan clearance. IV melphalan may also reduce the threshold for Carmustine lung toxicity.

Nalidixic acid:

When nalidixic acid and IV melphalan are given simultaneously, the incidence of severe haemorrhagic necrotic enterocolitis has been reported to increase in paediatric patients.

Vaccines:

Vaccinations with live organism vaccines are not recommended in immunocompromised individuals. See 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Melphalan causes suppression of ovarian function in premenopausal women, resulting in amenorrhoea in a significant number of patients. Reversible and irreversible testicular suppression have also been reported.

No fertility studies have been conducted in animals. However, there is evidence from some animal studies that melphalan can have an adverse effect on spermatogenesis. Therefore, it is possible that melphalan may cause temporary or permanent sterility in male patients.

Use in pregnancy

In view of its mutagenic properties and structural similarity to known teratogenic compounds, it is possible that melphalan could cause congenital defects in the offspring of patients treated with the drug.

Melphalan may cause foetal harm when administered to a pregnant woman.

As with all cytotoxic chemotherapy, adequate contraceptive precautions should be practised when either partner is receiving melphalan hydrochloride.

The use of melphalan hydrochloride should be avoided whenever possible during pregnancy, particularly during the first trimester. In any individual case the potential hazard to the foetus must be balanced against the expected benefit to the mother.

Although adequate animal studies have not been conducted with IV melphalan, oral and IV melphalan has been shown to be teratogenic and embryogenic in animal stdies. A single dose of 5 mg/kg (30 mg /m²) intraperitoneal (IP) given on day 8 or day 9 of gestation in the rat was embryolethal and teratogenic, and a single dose of 3 mg/kg IP (18 mg/m²) was teratogenic when administered on day 6. Malformations resulting from melphalan administration included alterations of the brain (underdevelopment, deformation, meningocele and encephalocele) and eye (anophthalmia and microphthalmos), reduction of the mandible and tail, as well as exomphaly (umbilical hernia).

In a repeat-dose embryotoxicity study in rats, (0.33, 1 & 3 mg/kg/day Per os (PO) on gestation days 7-17; total doses: 22, 66 and 198 mg/m² PO), respectively; cf. clinical dose of 16 mg/m² IV), all doses were maternotoxic (reduced weight gain, and mortality occurred at the high dose). Intrauterine deaths, reduced foetal and pup weights and pup weight gain over the lactation period were seen in the mid and high dose groups but pup survival over the lactation period was reduced at all doses. Melphalan showed a reduction in ossification at ≥1 mg/kg/day and an increased incidence of rib anomalies and impairment of pup development (delayed eruption of incisors, significantly different open-field behaviour) at the high dose.

No animal studies have been conducted to investigate the peri- and post-natal effects of melphalan.

Use in lactation

It is not known whether this drug is excreted in human milk. Mothers receiving melphalan hydrochloride should not breast-feed.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies have been conducted on the effects on the viability and the ability to operate machines. However, the possibility will have to be taken into consideration, that the alcohol quantity in these pharmaceutical medicinal product can impair the competency to drive and the ability to operate machines

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The following information on adverse reactions is based on data from both oral and IV administration of melphalan as a single agent, using several different dose schedules for treatment of a wide variety of malignancies.

Haematologic:

The most common side effect is bone marrow suppression, leading to leucopenia, thrombocytopenia and anaemia. White blood cell count and platelet count nadirs usually occur 2 to 3 weeks after treatment, with recovery in 4 to 5 weeks after treatment. Irreversible bone marrow failure has been reported. Acute leukaemia has also been reported (See Carcinogenicity).

Gastrointestinal:

Gastrointestinal disturbances such as nausea, vomiting and diarrhoea are very common. At high doses of melphalan, stomatitis is very common and rare at conventional doses. The incidence of diarrhoea, vomiting and stomatitis becomes the dose limiting toxicity in patients given high i.v. doses of melphalan in association with heamopoietic stem cell rescue. Cyclophosphamide pre-treatment appears to

reduce the severity of gastrointestinal damage induced by high-dose melphalan and the literature should be consulted for details. Oral ulceration occurs infrequently. Hepatic toxicity, including veno-occlusive disease, has been reported.

Hypersensitivity:
Acute hypersensitivity reactions including anaphylaxis were reported in 2.4% of 425 patients receiving melphalan for injection for myeloma (see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). These reactions were characterised by urticaria, pruritus, skin rashes, oedema, and in some patients, tachycardia, bronchospasm, dyspnoea, and hypotension. These patients appeared to respond to antihistamine and corticosteroid therapy. If a hypersensitivity reaction occurs, IV or oral melphalan should not be readministered since hypersensitivity reactions have also been reported with oral melphalan. Cardiac arrest has also been reported rarely in association with such events.

Miscellaneous:
Other reported adverse reactions include skin hypersensitivity, skin ulceration at injection site, skin necrosis rarely requiring skin grafting, maculopapular rashes, pruritus, vasculitis, allergic reaction, and interstitial pneumonitis. A subjective and transient sensation of warmth and/or tingling is very common.

Hepatic disorders ranging from abnormal liver function tests to clinical manifestations such as hepatitis and jaundice have been reported. Veno-occlusive disease has been reported in association with these cases.

There have been case reports of interstitial pneumonitis and pulmonary fibrosis. There have also been case reports of fatal pulmonary fibrosis and haemolytic anaemia occurring after melphalan treatment.

Alopecia is very common at high doses and common at conventional doses.

Temporary significant elevation of the blood urea has been seen in the early stages of melphalan therapy in myeloma patients with renal damage.

Muscular atrophy, muscle fibrosis, myalgia and increases in blood creatine phosphokinase are very commonly observed following isolated limb perfusion, while compartment syndrome is commonly observed. The incidence of muscle necrosis and rhabdomyolysis are not known in this setting

Reporting suspected adverse reactions after registration 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 at http://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Symptoms and Signs:
Overdoses resulting in death have been reported. Overdoses, including doses up to 290 mg/m², have produced the following symptoms: severe nausea and vomiting, decreased consciousness, convulsions, muscular paralysis, and cholinomimetic effects. Damage to the gastrointestinal lining may also ensue. Severe mucositis, stomatitis, colitis, diarrhoea, and haemorrhage of the gastrointestinal tract occur at high doses (>100 mg/m²). Elevations in liver enzymes and veno-occlusive disease occur infrequently. Significant hyponatremia caused by an associated inappropriate secretion of antidiuretic hormone (ADH) syndrome has been observed. Nephrotoxicity and adult respiratory distress syndrome have been reported rarely.

Treatment:
The principal toxic effect is bone marrow suppression, leading to leucopenia, thrombocytopenia and anaemia. Haematologic parameters should be closely followed for at least 4 weeks following overdosage until there is evidence of recovery. An uncontrolled study suggests that administration of autologous bone marrow or haematopoietic growth factors (ie. filgrastim) may shorten the period of pancytopenia. General supportive measures together with appropriate blood and platelet transfusions and antibiotics should be instituted as deemed necessary by the physician. This drug is not removed from plasma to any significant degree by haemodialysis or haemoperfusion. A paediatric patient survived a 254 mg/m² overdose treated with standard supportive care.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action
Cytotoxic and alkylating agent

Melphalan is a bifunctional alkylating agent. Formation of carbonium intermediates from each of the two bis- 2-chloroethyl groups enables alkylation through covalent binding with the 7- nitrogen of guanine on DNA, cross-linking two DNA strands and thereby preventing cell replication. Like other bifunctional alkylating agents, it is active against both resting and rapidly dividing tumour cells.

Clinical trials
A randomised trial compared prednisone plus IV melphalan to prednisone plus oral melphalan in the treatment of myeloma. As discussed below, overall response rates at week 22 were comparable; however, because of changes in trial design, conclusions as to the relative activity of the two formulations after week 22 are impossible to make.

Both arms received oral prednisone starting at 0.8 mg/kg per day with doses tapered over 6 weeks. Melphalan doses in each arm were:

Arm 1 Oral melphalan 0.15 mg/kg per day x 7 followed by 0.05 mg/kg per day when WBC began to rise.
Arm 2 IV melphalan 16 mg/m² once every 2 weeks x 4 (over 6 weeks) followed by the same dose every 4 weeks.

Doses of melphalan were adjusted according to the following criteria:

Table 1 : Criteria for dosage adjustment in a randomised clinical trial

WBC/mm³	Platelets	Percent of Full Dose
≥4000	≥100,000	100
≥3000	≥75,000	75
≥2000	≥50,000	50
<2000	<50,000	0

One hundred and seven patients were randomised to the oral melphalan arm and 203 patients to the IV melphalan arm. More patients had a poor-risk classification (58% versus 44%) and high tumour load (51% versus 34%) on the oral compared to the IV arm (P<0.04). Response rates at week 22 are shown in the following table:

Table 2: Response Rates at Week 22

Initial Arm	Evaluable Patients	Responders n (%)	P
Oral melphalan	100	44 (44%)	P>0.2
IV melphalan	195	74 (38%)	

Because of changes in protocol design after week 22, other efficacy parameters such as response duration and survival cannot be compared.

Severe myelotoxicity (WBC ≤1000 and/or platelets ≤25,000) was more common in the IV melphalan arm (28%) than in the oral melphalan arm (11%).

An association was noted between poor renal function and myelosuppression; consequently, an amendment to the protocol required a 50% reduction in IV melphalan dose if the BUN was ≥30 mg/dL (≥10.71 mmol/L). The rate of severe leucopenia in the IV arm in the patients with BUN over 30 mg/dL (≥10.71 mmol/L) decreased from 50% (8/16) before protocol amendment to 11% (3/28) (P = 0.01) after the amendment.

Before the dosing amendment, there was a 10% (8/77) incidence of drug-related death in the IV arm. After the dosing amendment, this incidence was 3% (3/108). This compares to an overall 1% (1/100) incidence of drug-related death in the oral arm.

5.2 PHARMACOKINETIC PROPERTIES

Absorption
The pharmacokinetics of melphalan after IV administration has been extensively studied in adult patients. Following injection, drug plasma concentrations declined rapidly in a biexponential manner with distribution phase and terminal elimination phase half-lives of approximately 10 and 75 minutes, respectively. Estimates of average total body clearance varied among studies, but typical values of approximately 7 to 9 mL/min per kg (250 to 325 mL/mln per m²) were observed. One study has reported that on repeat dosing of 0.5 mg/kg every 6 weeks, the clearance of melphalan decreased from 8.1 mL/min per kg after the first course, to 5.5 mL/min per kg after the third course, but did not decrease appreciably after the third course. Mean (±SD) peak melphalan plasma concentrations in myeloma patients given IV melphalan at doses of 10 or 20 mg/m² were 1.2 ± 0.4 and 2.8 ± 1.9 µg/mL, respectively.

Distribution
The steady-state volume of distribution of melphalan is 0.5 L/kg. Penetration into cerebrospinal fluid (CSF) is low. The extent of melphalan binding to plasma proteins ranges from 60% to 90%. Serum albumin is the major binding protein, while α1-acid glycoprotein appears to account for about 20% of the plasma protein binding.
Approximately 30% of the drug is (covalently) irreversibly bound to plasma proteins. Interactions with immunoglobulins have been found to be negligible.

Metabolism
Melphalan is metabolised primarily by chemical hydrolysis to monohydroxymelphalan and dihydroxymelphalan. Aside from these hydrolysis products, no other melphalan metabolites have been observed in humans.

Excretion
Melphalan is eliminated from plasma. Although the contribution of renal elimination to melphalan clearance appears to be low, one study noted an increase in the occurrence of severe leucopoenia in patients with elevated blood urea nitrogen (BUN) after 10 weeks of therapy.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity
Chromosome aberrations have been observed in patients being treated with Melphalan. Melphalan has been shown to cause chromatid and chromosome damage in human lymphocytes at a single dose of 20 mg IV (~10.6 mg/m², comparable to a therapeutic dose of 16 mg/m²) and in rat bone marrow cells at a single intramuscular dosage of 6 mg/m². Melphalan also showed mutagenic effects on germ cells in male mice at 17.1- 21.9 mg/m².

Carcinogenicity
Secondary malign ancies, including acute nonlymphocytic leukaemia, myeloproliferative syndrome, and carcinoma, have been reported in patients with cancer treated with alkylating agents (including melphalan). Some patients also received other chemotherapeutic agents or radiation therapy. Precise quantitation of the risk of myeloproliferative syndrome, or carcinoma is not possible. Melphalan, in common with other alkylating agents, has been reported to be leukaemogenic. There have been reports of acute leukaemia occurring after melphalan treatment for diseases such as amyloid, malignant melanoma, multiple myeloma, macroglobulinaemia, cold agglutinin syndrome and ovarian cancer. Published reports of leukaemia in patients who have received melphalan (and other alkylating agents) suggest that the risk of leukaemogenesis increases with chronicity of treatment and with cumulative dose.

A comparison of patients with ovarian cancer who received alkylating agents with those who did not showed that the use of alkylating agents, including melphalan, significantly increased the incidence of acute leukaemia.

The potential benefits from melphalan hydrochloride therapy must be weighed on an individual basis against the possible risk of the induction of a second malignancy.

Although adequate and well-controlled carcinogenicity studies have not been conducted in animals, there is clear evidence from animal studies that melphalan is carcinogenic. Intraperitoneal (IP) administration of melphalan in rats (5.4 or 10.8 mg/m²) and mice (2.25 or 4.5 mg/m²) three times per week for 6 months followed by a 12 months postdose observation produced peritoneal sarcoma in rats, and lung tumors and lymphosarcomas (males) in mice. Lung tumours were also increased in two other studies in mice (total dose: 144 mg/m² dermal given as 10 injections over a period of 10 weeks; 3.2-51 mg/m² IP given as 12 injections over a period of 4 weeks) while in one of these studies (dermal), skin papillomas were increased although nonsignificantly.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS
Melphalan Hydrochloride for injection 50 mg/vial : Povidone
Sterile diluent - 10 mL (For Melphalan Hydrochloride for Injection) :
Ethanol (96%) Ph. Eur
Water for injection Ph. Eur q.s. to 10 mL

6.2 Incompatibilities
Megval Injection is not compatible with infusion solutions containing dextrose and it is recommended that ONLY Sodium Chloride Intravenous Infusion 0.9% w/w be used

6.3 SHELF LIFE
36 Months

6.4 SPECIAL PRECAUTIONS FOR STORAGE
Store below 30° C.
Protect from light. Protect from moisture.

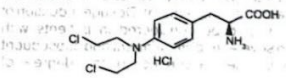
6.5 NATURE AND CONTENTS OF CONTAINER
Megval for Injection is supplied in a carton containing one single-use clear glass vial of freeze-dried melphalan hydrochloride equivalent to 50 mg melphalan and one 10 mL clear glass vial of sterile diluent.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
Megval Injection solution should be disposed in a manner appropriate for toxic chemicals, for example, high-temperature incineration.

6.7 PHYSICOCHEMICAL PROPERTIES
Melphalan hydrochloride, also known as L-phenylalanine mustard, phenylalanine mustard, L-PAM, or L-sarcolysin, is a phenylalanine derivative of nitrogen mustard. Melphalan hydrochloride is a bifunctional alkylating agent that is active against selected human neoplastic diseases. It is known chemically as 4-[bis (2-chloroethyl) amino]-L-phenylalanine. The molecular formula is C13H18 Cl2N2O2. HCl and the molecular weight is 341.67.

Melphalan is the active L-isomer of the compound and was first synthesised in 1953. Melphalan is practically insoluble in water and freely soluble in Methanol, soluble in Conc. HCl.

Chemical structure
The structural formula is:



CAS number
CAS: 3223-07-2

7 Manufactured by :
Emcure Pharmaceuticals Ltd.
Hinjawadi, Pune - 411057, India

8 DATE OF FIRST APPROVAL
N/A

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