VENTAVIS® 10 µg/mL

Nebulizer Solution

Important information, please read carefully!

Composition

1 mL nebulizer solution contains 10 micrograms iloprost (as iloprost trometamol).

One ampoule with 2 mL nebulizer solution contains 20 microgram iloprost (as iloprost trometamol).

The final alcohol content below 0.1% (v/v).

Pharmaceutical form

Nebulizer solution

Clear, colorless solution.

Pharmacological properties

Pharmacodynamic properties

Pharmacotherapeutic group: Platelet aggregation inhibitors excluding heparin
ATC code: B01A C11

Iloprost, the active ingredient of Ventavis, is a synthetic prostacyclin analogue. The following pharmacological effects have been observed in vitro:

- Inhibition of platelet aggregation, platelet adhesion and release reaction
- Dilatation of arterioles and venules
- Increase of capillary density and reduction of increased vascular permeability caused by mediators such as serotonin or histamine in the microcirculation
- Stimulation of endogenous fibrinolytic potential

The pharmacological effects after inhalation of Ventavis are:

Direct vasodilatation of the pulmonary arterial bed occurred with consecutive significant improvement of pulmonary artery pressure, pulmonary vascular resistance and cardiac output as well as mixed venous oxygen saturation.

In a small, randomized, double-blind, placebo-controlled study (the STEP trial), 34 patients treated with bosentan 125 mg twice per day for at least 16 weeks tolerated the addition of inhaled iloprost (up to 5 microgram 6 to 9 times per day during waking hours). The mean daily inhaled dose was 27 microgram and the mean number of inhalations per day was 5.6. The safety trends in patients receiving concomitant bosentan and iloprost were consistent with those observed in the larger experience of the phase 3 study in patients receiving only iloprost.

No clinical trial data are available comparing directly in intra-patient observations the acute haemodynamic response after intravenous to that after inhaled iloprost. The haemodynamics observed suggest an acute response with preferential effect of inhaled treatment on the pulmonary vessels. The pulmonary vasodilatory effect of each single inhalation levels off within one to two hours. However, the predictive value of these acute haemodynamic data are considered to be of limited value as acute response does not in all cases correlate with long term benefit of treatment with inhaled iloprost.

<u>Efficacy in adult patients with pulmonary hypertension</u>

A randomised, double blind, multi center, placebo-controlled phase III trial (study RRA02997) has been conducted in 203 adult patients (inhaled iloprost : N = 101; placebo n = 102) with stable pulmonary hypertension. Inhaled iloprost (or placebo) was added to patients current therapy, which could include a combination of anticoagulants, vasodilators (e.g. calcium channel blockers), diuretics, oxygen, and digitalis, but not PGI2 (prostacyclin or its analogues). 108 of the patients included were diagnosed with primary pulmonary hypertension, 95 were diagnosed with secondary pulmonary hypertension of which 56 were associated with chronic thromboembolic disease, 34 with connective tissue disease (including CREST and scleroderma) and 4 were considered appetite suppressant drug related. The baseline 6 minute walk test values reflected a moderate exercise limitation : in the iloprost group the mean was 332 meters (median value : 340 meters) and in the placebo group the mean was 315 meters (median value : 321 meters). In the iloprost group, the median daily inhaled dose was 30 µg (range 12.5 to 45 µg/day). The primary efficacy endpoint defined for this study, was a combined response criterion consisting of improvement in exercise capacity (6 minute walk test) at 12 weeks by at least 10 % versus baseline, and improvement by at least one NYHA class at 12 weeks versus baseline, and no deterioration of pulmonary hypertension or death at any time before 12 weeks. The rate of responders to iloprost was 16.8 % (17/101) and the rate of responders in the placebo group was 4.9 % (5/102) (p=0.007).

In the iloprost group, the mean change from baseline after 12 weeks of treatment in the 6 minute walking distance was an increase of 22 meters (-3.3 meters in the placebo group, no data imputation for death or missing values).

In the iloprost group the NYHA class was improved in 26 % of patients (placebo: 15 %) (p=0.032), unchanged in 67.7 % of patients (placebo : 76 %) and deteriorated in 6.3 % of patients (placebo : 9 %). Invasive haemodynamic parameters were assessed at baseline and after 12 weeks treatment.

A subgroup analysis showed that no treatment effect was observed as compared to placebo on the 6 minute walk test in the subgroup of patients with secondary pulmonary hypertension. A mean increase in the 6 minute walk test of 44.7 meters from a baseline mean value of 329 meters vs. a change of –7.4 meters from a baseline mean value of 324 meters in the placebo group (no data imputation for death or missing values) was observed in the subgroup of 49 patients with primary pulmonary hypertension receiving treatment of inhaled iloprost for 12 weeks (46 patients in the placebo group).

No study has been performed with Ventavis in children with pulmonary hypertension.

Pharmacokinetic properties

Absorption

When iloprost is administered via inhalation in patients with pulmonary hypertension (iloprost dose at the mouthpiece: 5 micrograms inhalation time between 4.6-10.6 min), peak serum levels of 100 to 200 picograms/mL were observed at the end of inhalation. These levels decline with half-lives between approximately 5 and 25 minutes. Within 30 minutes to 2 hours after the end of inhalation, iloprost is not detectable in the central compartment (limit of quantification 25 picograms/mL).

Distribution

No studies performed following inhalation.

Following intravenous infusion, the apparent steady-state volume of distribution was 0.6 to 0.8 L/kg in healthy subjects. Total plasma protein binding of iloprost is concentration-independent in the range of 30 to 3000 picograms/mL and amounts to approximately 60 %, of which 75 % is due to albumin binding.

Metabolism

No studies to investigate the metabolism of iloprost were performed following inhalation of Ventavis.

In vitro studies suggest, however, that metabolism of iloprost in the lungs is similar after intravenous administration or inhalation.

After intravenous administration, iloprost is extensively metabolized via ß-oxidation of the carboxyl side chain. No unchanged substance is eliminated. The main metabolite is tetranor-iloprost, which is found in the urine in free and conjugated form. Tetranor-iloprost is pharmacologically inactive as shown in animal experiments.

In vitro studies revealed that cytochrome P450-dependent metabolism plays only a minor role in the biotransformation of iloprost.

Elimination

No studies performed following inhalation.

In subjects with normal renal and hepatic function, the disposition of iloprost following intravenous infusion is characterized in most cases by a two-phase profile with mean half-lives of 3 to 5 minutes and 15 to 30 minutes.

A mass-balance study was done using ^{3}H-iloprost in healthy subjects. Following intravenous infusion, the recovery of total radioactivity is 81 %, and the respective recoveries in urine and feces are 68 % and 12 %. The metabolites are eliminated from plasma and with urine in 2 phases, for which half-lives of about 2 and 5 hours (plasma) and 2 and 18 hours (urine) have been calculated.

Characteristics in specific patient groups

Renal dysfunction:

In a study with intravenous infusion of iloprost, patients with end stage renal failure undergoing intermittent dialysis treatment are shown to have a significantly lower clearance (mean CL = 5 ± 2 mL/minute/kg) than that observed in patients with renal failure not undergoing intermittent dialysis treatment (mean CL = 18 ± 2 mL/minute/kg).

Hepatic dysfunction:

Because iloprost is extensively metabolized by the liver, the plasma levels of the drug are influenced by changes in hepatic function. In an intravenous study, results were obtained involving 8 patients suffering from liver cirrhosis. The mean clearance of iloprost is estimated to be 10 mL/minute/kg.

Age and gender:

Age and gender are not of clinical relevance to the pharmacokinetics of iloprost.

Preclinical safety data

Systemic toxicity

In acute toxicity studies, single intravenous and oral doses of iloprost caused severe symptoms of intoxication or death (IV) at dosages about two orders of magnitude above the intravenous therapeutic dose. Considering the high pharmacological potency of iloprost and the absolute doses required for therapeutic purposes the results obtained in acute toxicity studies do not indicate a risk of acute adverse effects in humans. As expected for a prostacyclin, iloprost produced hemodynamic effects (vasodilatation, reddening of skin, hypotension, inhibition of platelet function, respiratory distress) and general signs of intoxication such as apathy, gait disturbances, and postural changes.

In systemic toxicity studies with repeated (continuous) i.v. infusion, a slight reduction of the blood pressure occurred at doses above 14 ng/kg/min. and severe undesired effects (hypotension, disturbance of respiratory function) appeared only after extremely high dosages.

Continuous i.v./s.c. infusion of iloprost up to 26 weeks in rodents and non-rodents at dose levels which exceeded the human therapeutic systemic exposure between 14 and 47 times (based on plasma levels) did not cause any organ toxicity. Only expected pharmacological effects like hypotension, reddening of skin, dyspnea, increased intestinal motility were observed.

Based on C_{max} values in rats the systemic exposure in these parenteral studies was approximately 3.5 times higher than the maximum achievable exposure after inhalation. This highest achievable dose of 48.7 micrograms/kg/day was also the “no observed adverse effect level” (NOAEL) as evaluated in inhalation toxicity studies in rats up to 26 weeks. Following inhalation the systemic exposure based on AUC values in rats exceeded the corresponding therapeutic exposure in human patients by approximately 13 times.

Genotoxic potential, tumorigenicity

In vitro and in vivo studies for genotoxic effects have not produced any evidence for a mutagenic potential.

No tumorigenic potential of iloprost was observed in tumorigenicity studies in rats and mice.

Reproduction toxicology

In embryo- and fetotoxicity studies in rats continuous intravenous administration of iloprost led to anomalies of single phalanges of the forepaws in a few fetuses/pups without dose dependence.

These alterations are not considered as teratogenic effects, but are most likely related to iloprost induced growth retardation in late organogenesis due to hemodynamic alterations in the fetoplacental unit. No disturbance of postnatal development and reproductive performance was seen in the offspring that were raised, indicating that the observed retardation in rats was compensated during the postnatal development. In comparable embryotoxicity studies in rabbits and monkeys no such digit anomalies or other gross-structural anomalies were observed even after considerably higher dose levels which exceeded the human dose multiple times.

In rats a passage of low levels of iloprost and/or metabolites into the milk was observed (less than 1% of iloprost dose given intravenously). No disturbance of post-natal development and reproductive performance was seen in animals exposed during lactation.

Local tolerance, contact sensitizing and antigenicity potential

In inhalation studies in rats, the administration of an iloprost formulation with a concentration of 20 micrograms/mL up to 26 weeks did not cause any local irritation of the upper and lower respiratory tract.

A dermal sensitization (maximization test) and an antigenicity study in guinea pigs showed no sensitizing potential.

Indication

Treatment of patients with primary pulmonary hypertension or secondary pulmonary hypertension due to connective tissue disease or drug-induced, in moderate or severe stages of the disease.

In addition, treatment of moderate or severe secondary pulmonary hypertension due to chronic pulmonary thromboembolism, where surgery is not possible.

Dosage and method of administration

Method of administration

Ventavis should only be initiated and monitored by a physician experienced in the treatment of pulmonary hypertension.

Ventavis is intended for inhalation use by nebulisation

The ready-to-use Ventavis 10 microgram / mL nebulizer solution is administered with a suitable inhalation device (nebulizer) as recommended in the section 'Instructions for use/handling'.
Previous therapy should be adjusted to individual needs (see section 'Interaction with other medicaments and other forms of interaction').

Dosage regimen

Adults

At initiation of Ventavis 10 microgram / mL treatment the first inhaled dose should be 2.5 micrograms iloprost (as delivered at the mouthpiece). If this dose is well tolerated, dosing should be increased to 5.0 microgram and maintained at that dose. In case of poor tolerability of the 5.0 microgram dose, the dose should be reduced to 2.5 micrograms.

Two compressed air nebuliser systems, haloLite and Prodose, have been shown to be suitable nebulisers for the administration of Ventavis. With both systems the mass median aerodynamic diameter of the aerosol droplet (MMAD) with iloprost was between 2.6 and 2.7 μm. For each inhalation session the content of one 2-ml ampoule of ventavis will be transferred into the nebuliser medication chamber immediately before use. HaloLite and Prodose are dosimetric systems. They stop automatically after the pre-set dose has been delivered. The inhalation time depends on the patient's breathing pattern.

Device	Dose of Iloprost at mouthpiece	Estimated Inhalation time (frequency of 15 breaths per minute)
HaloLite	2.5 μg 5 μg	4 to 5 min 8 to 10 min
Prodose	2.5 μg 5 μg	4 to 5 min 8 to 10 min

For a dose of 5 μg iloprost at mouthpiece it is recommended to complete two inhalation cycles with 2.5 μg pre-set dose program with a filling of one 2-ml ampoule.

The efficacy and tolerability of inhaled iloprost when administered with other nebulising system which provide different nebulisation characteristics of iloprost solution, have not been established.

Daily dose

The dose per inhalation session should be administered 6 to 9 times per day according to the individual need and tolerability.

Depending on the desired dose at the mouthpiece and on the nebulizer, the duration of an inhalation session is approximately 4 to 10 minutes.

Duration of treatment

The duration of treatment depends on clinical status and is left to the physician's discretion. Should patients deteriorate on this treatment intravenous prostacyclin treatment should be considered

Additional information on special populations

Children and adolescents

The experience in children and adolescents (patients below 18 years of age) is limited. Therefore, Ventavis is not recommended for use in this population.

Patients with hepatic impairment

Iloprost elimination is reduced in patients with hepatic dysfunction (see section 'Pharmacokinetic properties').

To avoid undesired accumulation over the day, special caution has to be exercised with these patients during initial dose titration. Initially, doses of 2.5 micrograms should be administered with dosing intervals of 3 - 4 hours (corresponds to administration of max. 6 times per day). Thereafter, dosing intervals may be shortened cautiously based on individual tolerability. If a further increase in the dose up to 5.0 micrograms is indicated, again dosing intervals of 3 - 4 hours should be chosen initially and shortened according to individual tolerability. An accumulation of iloprost following treatment over several days is not likely due to the overnight break in administration of the medicinal product.

Patients with renal impairment

There is no need for dose adaptation in patients with a creatinine clearance > 30 mL/min (as determined from serum creatinine using the Cockroft and Gault formula). Patients with a creatinine clearance of ≤ 30 mL/min were not investigated in the clinical trials with Ventavis. Based on data with intravenously administered iloprost the elimination is reduced in patients with renal failure requiring dialysis. For dosing recommendations see "Patients with hepatic impairment".

Special warning and precautions for use

Ventavis nebulizer solution should not come into contact with skin and eyes; oral ingestion of Ventavis solution should be avoided. During nebulization sessions a facial mask must be avoided and only a mouthpiece should be used.

Risk of syncope

Physicians should be alert to the presence of concomitant conditions or drugs that might increase the risk of syncope (see section 'Interaction with other medicinal products and other forms of interaction').

Syncope is also a common symptom of the disease itself. Patients who experience syncope in association with pulmonary hypertension should avoid any exceptional straining, for example during physical exertion. Before physical exertion it might be useful to inhale. If syncope occurs on rising, it may be useful to take the first dose of the day on waking, while still recumbent. The pulmonary vasodilatory effect of inhaled iloprost is of short duration (one to two hours).The increased occurrence of syncopes can reflect therapeutic gaps and/or deterioration of the disease. The need to adapt and/or change the therapy should be considered (see section 'Undesirable effects').

Hypotension

Vital signs should be monitored while initiating Ventavis. In patients with low systemic blood pressure, care should be taken to avoid further hypotension. Ventavis should not be initiated in patients with systolic blood pressure less than 85 mm Hg.

Bronchospasm

Ventavis inhalation might entail the risk of inducing bronchospasm, especially in patients with bronchial hyperreactivity (see section 'Undesirable effects'). The benefit of Ventavis has not been established in patients with concomitant Chronic Obstructive Pulmonary Disease (COPD) and severe asthma. Patients with concomitant acute pulmonary infections, COPD, and severe asthma should be carefully monitored.

Chronic Thromboembolic Pulmonary Hypertension (CTEPH)

Ventavis should not be used as the first treatment option in thromboembolic pulmonary hypertension if surgery is feasible.

Pulmonary veno-occlusive disease (PVOD)

Should signs of pulmonary edema occur when inhaled iloprost is administered in patients with pulmonary hypertension, the possibility of associated pulmonary veno-occlusive disease should be considered. The treatment should be stopped.

In case of interruption of Ventavis therapy, the risk of rebound effect is not formally excluded. Careful monitoring of the patient should be performed, when inhaled iloprost therapy is stopped and an alternative treatment should be considered in critically ill patients.

The use of Ventavis is not recommended in patients with unstable pulmonary hypertension, with advanced right heart failure. In case of deterioration or worsening of right heart failure transfer to other medicinal products should be considered.

Patients with hepatic and renal impairment

Iloprost elimination is reduced in patients with hepatic dysfunction and in patients with renal failure requiring dialysis as demonstrated by data with intravenously administrated iloprost (see section 'Pharmacokinetic properties'). A cautious initial dose titration using dosing intervals of 3-4 hours is recommended (see section 'Dosage and method of administration').

Pregnancy and lactation

There are insufficient data from the use of Ventavis in pregnant women. Therefore, women of child bearing potential should use effective contraceptive measures during treatment with Ventavis. If a pregnancy occurs, Ventavis should only be used following careful risk-benefit evaluation (see section 'Pregnancy and lactation').

It is not known whether iloprost/metabolites are excreted in human milk. Therefore women should not breast-feed during treatment with Ventavis (see section 'Pregnancy and lactation').

Prolonged oral treatment with iloprost clathrate in dogs up to one year was associated with slightly increased fasted serum glucose levels. It cannot be excluded that this is also relevant to man on prolonged Ventavis therapy.

To minimise accidental exposure, it is recommended to use Ventavis with nebulisers with inhalation-triggered system (HaloLite/Prodose), and keep the room well ventilated.

Pregnancy and lactation

Pregnancy

Women with pulmonary hypertension (PH) must avoid pregnancy as it may lead to life-threatening exacerbation of the disease.

There are insufficient data from the use of Ventavis in pregnant women. Studies in rats with continuous intravenous iloprost administration have shown digit anomalies in a few fetuses/pups without dose dependence. These effects are not regarded as teratogenic but are most likely related to iloprost-induced growth retardation due to hemodynamic alterations in the fetoplacental unit and have not been observed in other species (see section 'Preclinical safety data'). The potential risk for humans is unknown.

Therefore, women of child-bearing potential should use effective contraceptive measures during treatment with Ventavis. If a pregnancy occurs, Ventavis should only be used following careful risk-benefit evaluation (see section 'Special warnings and precautions for use').

Lactation

It is not known whether iloprost/metabolites are excreted in human milk. There is evidence from non-clinical data that iloprost and/or metabolites are excreted in milk to a low extent (less than 1% of iloprost dose given intravenously). Therefore women should not breast-feed during treatment with Ventavis (see section 'Special warnings and precautions for use' and section 'Preclinical safety data').

Overdose

Symptoms

Cases of overdose were reported. Frequently observed symptoms following overdose are dizziness, headache, flushing, nausea, jaw pain or back pain. Hypotension, an increase of blood pressure, bradycardia or tachycardia, vomiting, diarrhea and limb pain might also be possible.

Therapy

A specific antidote is not known.
Interruption of the iloprost administration, monitoring and symptomatic measures are recommended.

Effects on ability to drive or use machines

Care should be exercised during initiation of therapy until any effects on the individual have been determined. In patients experiencing hypotensive symptoms such as dizziness, ability to drive or operate machines may be seriously affected.

Undesirable effects

Summary of the safety profile

In addition to local effects resulting from administration of iloprost by inhalation such as cough, adverse reactions with iloprost are related to the pharmacological properties of prostaglandins. The most frequently observed adverse reactions (≥ 20 %) in clinical trials include vasodilatation, headache, and cough. The most serious adverse reactions were hypotension, bleeding events, and bronchospasm.

Tabulated list of adverse reactions

The adverse drug reactions observed with Ventavis are represented in the table below. They are classified according to System Organ Class (MedDRA version 14.0). The most appropriate MedDRA term is used to describe a certain reaction and its synonyms and related conditions.

The adverse drug reactions (ADRs) reported below are based on pooled clinical trial data from phase II and III clinical trials involving 131 patients taking Ventavis 10 microgram / mL and on data from post-marketing surveillance.

Adverse drug reactions from clinical trials are classified according to their frequencies. Frequency groupings are defined according to the following convention: very common: ≥ 1/10 and common: ≥ 1/100 to < 1/10.

The ADRs identified only during post marketing surveillance, and for which a frequency could not be estimated, are listed under "not known".

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1: Adverse drug reactions reported in patients treated with Ventavis

System Organ Class (MedDRA)	Very common (≥ 1/10)	Common (≥ 1/100 to <1/10)	Not known
Blood and lymphatic system disorders	Bleeding events*§		Thrombocytopenia
Immune system disorders			Hypersensitivity
Nervous system disorders	Headache	Dizziness	
Cardiac disorders		Tachycardia Palpitations	
Vascular disorders	Vasodilation	Hypotension* Syncope§	
Respiratory, thoracic and mediastinal disorders	Chest pain Cough	Dyspnea Pharyngolaryngeal pain Throat irritations	Bronchospasm* / Wheezing Nasal congestion

System Organ Class (MedDRA)	Very common (≥ 1/10)	Common (≥ 1/100 to <1/10)	Not known
Gastrointestinal disorders	Nausea	Diarrhea Vomiting Mouth and tongue irritation including pain	Dysgeusia
Skin and subcutaneous tissue disorders		Rash	
Musculoskeletal, connective tissue and bone disorders	Pain in jaw/trismus	Back pain	
General disorders and administration site conditions	Peripheral edema		

* life-threatening and/or fatal cases have been reported

§ see section 'Description of selected adverse reaction'

Description of selected adverse reactions

As expected in patients with pulmonary hypertension, syncopes were common, and did not differ significantly between the treatment groups in frequency (see section 'Special warnings and precautions for use').

Bleeding events (mostly epistaxis and hemoptysis) were very common as expected in this patient population with a high proportion of patients taking anticoagulant comedication. The risk of bleeding may be increased in patients when inhibitors of platelet aggregation or anticoagulants are given concomitantly (see section 'Interaction with other medicinal products and other forms of interaction'). Fatal cases of cerebral and intracranial hemorrhage have been reported.

In clinical trials peripheral edema was reported in 12.2% of patients on iloprost and 16.2 % of patients on placebo. Peripheral edema is a very common symptom of the disease itself, but it may also be related to the therapy.

Reporting of suspected adverse drug reaction

Reporting suspected adverse reaction after product authorization is crucial for ongoing benefit-risk monitoring. Healthcare professionals are requested to report any suspected adverse reactions to PT Bayer Indonesia through email at drugsafety.indonesia@bayer.com.

Contraindications

- Conditions where the effects of Ventavis on platelets might increase the risk of hemorrhage (e.g. active peptic ulcers, trauma, intracranial hemorrhage)
- Severe coronary heart disease or unstable angina
- Myocardial infarction within the last six months
- Decompensated cardiac failure if not under close medical supervision
- Severe arrhythmias
- Suspected pulmonary congestion
- Cerebrovascular events [e.g. transient ischemic attack, stroke] within the last 3 months
- Pulmonary hypertension due to venous occlusive disease
- Congenital or acquired valvular defects with clinically relevant myocardial function disorders not related to pulmonary hypertension
- Hypersensitivity to iloprost or to any of the excipients

Interaction with other medicinal products and other forms of interaction

Iloprost may increase the antihypertensive effect of vasodilating and antihypertensive agents (see section 'Special warnings and precautions for use'). Caution is recommended in case of co-administration of Ventavis with vasodilating or antihypertensive agents as dose adjustment might be required.

Because iloprost inhibits platelet function, its use with anticoagulants (such as heparin, coumarin-type anticoagulants), or other inhibitors of platelet aggregation (such as acetylsalicylic acid, non-steroidal anti-inflammatory drugs, non-selective phosphodiesterase inhibitors, [like theophylline, pentoxifylline, dipyridamole, trapidil or ibudilast] selective phosphodiesterase 3 [PDE3] inhibitors [like amrinone, enoximone, milrinone, cilostazol, anagrelide] and nitro vasodilators) may enhance iloprost-mediated platelet inhibition, thereby increasing the risk of bleeding (see section 'undesirable effects'). If bleeding occurs, iloprost administration should be stopped. A careful monitoring of the patients taking anticoagulants or other inhibitors of platelet aggregation according to common medical practice is recommended.

Oral premedication with acetylsalicylic acid up to 300 mg per day over a period of 8 days had no impact on the pharmacokinetics of iloprost.

In an animal study, it was found that iloprost may result in a reduction in tissue-type plasminogen activator (t-PA) steady-state plasma concentration.

The results of human studies show that iloprost infusions do not affect the pharmacokinetics of multiple oral doses of digoxin in patients and iloprost has no impact on the pharmacokinetics of co-administered t-PA.

Although, clinical studies have not been conducted, in vitro studies investigating the inhibitory potential of iloprost on the activity of cytochrome P450 enzymes revealed that no relevant inhibition of drug metabolism via these enzymes by iloprost have to be expected.

Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

Instruction for use / handling

For each inhalation session a new ampoule of Ventavis should be used. The content of the ampoule has to be completely transferred into the nebulizer chamber immediately before use.

Nebulizer solution not used in one inhalation session has to be discarded. In addition, instructions for hygiene and cleaning of the nebulizers provided by the device manufacturers should be followed carefully.

Use with nebulizers:

In general suitable nebulizers to be used for the inhalation therapy with Ventavis 10 microgram/mL nebulizer solution are registered according to the regional medical device regulations and work with compressed air, ultrasound or vibrating mesh technology.

Nebulizers suitable for inhalation Ventavis 10 microgram/mL fulfill the following requirements:

The nebulizing devices deliver 2.5 microgram or 5 microgram iloprost at the mouthpiece in a time period of approximately 4 to 10 minutes. The Mass Median Aerodynamic Diameter (MMAD) of the aerosol is between 1 and 5 micrometer.

If switching to a different type of nebulizer supervision by the treating physician is necessary.

To minimize accidental exposure, it is recommended to use Ventavis with nebulizers with a filter or inhalation-triggered systems, and to keep the room well ventilated.

List of excipients

Ethanol
Hydrochloric acid
Sodium chloride
Trometamol
Water for injections

Storage

Store all drugs properly and keep them out of reach of children.
Store below 30°C.

Presentation

Box, 30 ampoules @ 2 ml
Reg. No.: DKIXXXXXXXXXXX

Harus dengan resep dokter

Imported by:
PT Bayer Indonesia,
Depok-Indonesia

Manufactured by:
Berlimed S.A,
Spain

LEMBAR INFORMASI UNTUK PASIEN
VENTAVIS
Iloprost (sebagai Iloprost trometamol)
Cairan Nebulizer
VENTAVIS 10 microgram / mL

Bacalah semua bagian lembar informasi ini dengan seksama sebelum Anda menggunakan obat, karena lembar informasi ini mengandung informasi penting untuk Anda.
Simpanlah lembar informasi ini. Anda mungkin perlu membacanya kembali.
Jika Anda memiliki pertanyaan lebih lanjut, tanyakan kepada dokter atau apoteker Anda.
Obat ini hanya diresepkan untuk Anda. Jangan berikan obat ini kepada orang lain. Hal ini dapat membahayakan mereka, walaupun gejala penyakit mereka sama dengan Anda.

Jika Anda mengalami gejala efek samping, segera hubungi dokter atau apoteker Anda. Termasuk efek samping yang mungkin tidak tercantum dalam lembar informasi ini.

Apa saja isi lembar informasi ini

Ventavis 10 microgram/mL cairan nebulizer

Bahan aktif iloprost

1. APAKAH VENTAVIS ITU DAN APA KEGUNAANNYA

Apa itu Ventavis ?
Ventavis adalah cairan nebulizer. Cairan dirubah menjadi kabut aerosol dengan alat khusus yang disebut nebulizer.

Bagaimana cara kerja Ventavis ?
Iloprost zat aktif Ventavis mengimitasi zat alami dalam tubuh yang disebut prostasiklin. Ventavis dan prostasiklin menghambat pemblokiran atau penyempitan

pembuluh darah yang tidak diinginkan dan memungkinkan lebih banyak darah mengalir melalui pembuluh darah.

Menghirup kabut aerosol membawa Ventavis ke paru-paru, di mana ia dapat bekerja paling efektif di pembuluh darah. Peningkatan aliran darah menyebabkan pasokan oksigen yang lebih baik ke tubuh dan mengurangi ketegangan pada jantung

Kegunaan Ventavis :
Ventavis digunakan untuk mengobati kasus hipertensi pulmonal primer sedang dan berat. Kondisi di mana tekanan darah terlalu tinggi di pembuluh darah antara jantung dan paru-paru.

Ventavis juga digunakan untuk mengobati kasus hipertensi pulmonal sekunder sedang atau berat, yang disebabkan oleh penyakit jaringan ikat (kondisi peradangan), atau penggunaan obat lain.

Ventavis juga digunakan untuk mengobati hipertensi pulmonal sekunder sedang atau berat bila disebabkan oleh bekuan darah di dalam paru-paru, di mana tidak mungkin dilakukan pembedahan.

2. APA YANG PERLU ANDA KETAHUI SEBELUM MENGGUNAKAN VENTAVIS

Jangan gunakan Ventavis

- **Jika Anda berisiko mengalami pendarahan** – misalnya tukak lambung aktif (tukak lambung atau bagian awal usus halus, cedera, pendarahan di dalam tengkorak.)
- **Jika Anda memiliki masalah jantung**, seperti:
    - penyakit jantung koroner yang parah atau angina tidak stabil (penyakit jantung yang disebabkan oleh aliran darah yang buruk ke otot-otot jantung); gejala dapat berupa nyeri dada,
    - infark miokard (serangan jantung) dalam enam bulan terakhir,
    - gagal jantung dekompensasi (jantung lemah) yang tidak dalam pengawasan medis ketat,
    - aritmia berat (detak jantung tidak teratur yang parah),
    - cacat bawaan atau didapat dari katup jantung (bawaan atau didapat) yang menyebabkan jantung bekerja dengan buruk (tidak terkait dengan hipertensi pulmonal).
- **Jika Anda memiliki dugaan kongesti paru** (penumpukan cairan di paru-paru dengan kesulitan bernapas).
- **Jika Anda pernah mengalami kejadian serebrovaskular dalam 3 bulan terakhir** (misalnya stroke, serangan iskemik transien atau kejadian lain yang mengurangi suplai darah ke otak).

- **Jika penyakit Anda disebabkan oleh penyakit oklusi vena** (pembuluh darah yang tersumbat atau menyempit).

- **Jika Anda alergi** (hipersensitif) terhadap iloprost atau bahan lain dari Ventavis (lihat bagian 'kemasan dan informasi lainnya').

Berhati-hatilah menggunakan Ventavis

Jangan biarkan cairan Ventavis mengenai kulit atau mata Anda. Jika terkena, segera bilas kulit atau mata Anda dengan air yang banyak.

Jangan minum atau menelan cairan Ventavis. Jika Anda menelannya secara tidak sengaja, minumlah banyak air dan beri tahu dokter Anda.

- Pada awal terapi Ventavis, dokter Anda akan memantau Anda dengan cermat.

Jika Anda menderita tekanan darah rendah, dokter Anda akan memberikan perhatian khusus untuk menghindari penurunan lebih lanjut dari tekanan darah Anda. Jika tekanan darah Anda terlalu rendah (kurang dari 85 mm Hg untuk tekanan darah sistolik), Anda sebaiknya tidak memulai terapi dengan Ventavis.

Secara umum, Anda perlu **perawatan khusus untuk mencoba dan menghindari efek tekanan darah rendah, seperti sinkop (episode pingsan) atau pusing:**

  - Beri tahu dokter Anda jika Anda sedang mengonsumsi obat lain karena penurun tekanan darah efek Ventavis dapat meningkat (lihat bagian di bawah 'Penggunaan bersamaan obat lain')

  - Sinkop (episode pingsan) juga merupakan gejala umum dari penyakit yang mendasari itu sendiri. Jika Anda cenderung mengalami sinkop hindari mengejan yang luar biasa, misalnya selama aktivitas fisik; mungkin berguna untuk menghirup Ventavis sebelum aktivitas fisik.

  - Efek terapeutik inhalasi Ventavis berlangsung singkat (satu hingga dua jam). **Jika sinkop terjadi lebih sering, beri tahu dokter Anda**. Peningkatan kejadian sinkop dapat mencerminkan kesenjangan terapeutik dan/atau perburukan penyakit. Dokter Anda mungkin mempertimbangkan untuk menyesuaikan dosis Anda dan/atau mengubah pengobatan Anda.

- Menghirup Ventavis dapat memicu **bronkospasme** (penyempitan saluran napas dengan kemungkinan kesulitan bernapas), terutama pada pasien dengan masalah yang berkaitan dengan paru-paru (lihat juga bagian 'Kemungkinan efek samping'). Manfaat Ventavis belum ditetapkan pada pasien dengan penyakit paru obstruktif kronik (PPOK, penyakit paru kronis) dan asma berat.

  Jika Anda memiliki infeksi paru-paru akut, penyakit paru obstruktif kronik, atau asma parah, beri tahu dokter Anda. Dia akan memastikan bahwa Anda akan diawasi secara ketat.

- **Jika bekuan darah di paru-paru menyebabkan hipertensi pulmonal Anda (hipertensi pulmonal karena tromboemboli kronis) dan pembedahan dapat dilakukan,** Ventavis tidak boleh digunakan sebagai pengobatan pertama. Dokter Anda akan memberi tahu Anda, jika ini berlaku untuk Anda.

- **Jika Anda mengalami kesulitan bernapas, batuk berdarah, keringat berlebihan, ini mungkin merupakan tanda-tanda edema paru** (air di paru-paru). Berhenti menggunakan Ventavis dan beri tahu dokter Anda segera. Ia akan memeriksa penyebabnya (misalnya penyakit oklusi vena pulmonal yang terkait (pembuluh darah yang tersumbat atau menyempit di paru-paru)) dan mengambil tindakan yang tepat.

  Ventavis tidak direkomendasikan pada pasien hipertensi pulmonal yang tidak stabil yang disertai dengan gagal jantung kanan yang parah. Jika gagal jantung kanan memburuk perlu dipertimbangkan untuk penggunaan obat lain.

Jika Anda memiliki masalah hati atau ginjal yang sangat parah, yang memerlukan dialisis, beri tahu dokter Anda. Anda mungkin secara bertahap diperkenalkan dengan dosis Ventavis yang ditentukan menggunakan interval pemberian dosis 3 sampai 4 jam (lihat bagian 'Cara menggunakan Ventavis').

Anak-anak dan remaja

Ventavis tidak dianjurkan pada anak-anak atau remaja di bawah usia 18 tahun karena sedikit yang diketahui tentang bagaimana kelompok usia ini merespons terapi Ventavis.

Penggunaan bersamaan obat lain

Ventavis dan obat-obatan tertentu lainnya dapat mempengaruhi satu sama lain dalam bekerja di tubuh Anda. Beritahu dokter Anda, jika Anda mengkonsumsi:

- **Agen vasodilatasi dan antihipertensi (obat yang digunakan untuk memperlebar pembuluh darah, untuk mengobati tekanan darah tinggi dan beberapa kondisi jantung);** lihat bagian 'Sebelum Anda menggunakan Ventavis/Berhati-hatilah menggunakan Ventavis'). Tekanan darah Anda mungkin turun lebih rendah. Perhatian dianjurkan jika Ventavis digunakan bersamaan dengan obat-obatan ini. Dokter Anda mungkin mengubah dosisnya.
- **Obat-obatan yang mengencerkan darah atau menghambat pembekuan darah, termasuk**
  - asam asetilsalisilat [ASA - senyawa yang ditemukan dalam banyak obat-obatan yang menurunkan demam dan meredakan nyeri],
  - heparin,
  - antikoagulan tipe kumarin [misalnya warfarin, phenprocoumon],
  - obat antiinflamasi nonsteroid,
  - inhibitor phosphodiesterase non-selektif [misalnya teofilin, pentoxifylline, dipyridamole, trapidil ibudilast],
  - [PDE 3] inhibitor phosphodiesterase [misalnya amrinon, enoksimone, milrinone, cilostazol, anagrelide] dan
  - nitro vasodilator.

Risiko perdarahan dapat meningkat. Jika Anda menggunakan obat-obatan ini, beri tahu dokter Anda. Dokter Anda akan memantau Anda dengan cermat. Jika Anda mengalami pendarahan Anda harus segera menghentikan penggunaan dan segera menghubungi dokter Anda.

Tablet dengan asam asetilsalisilat hingga 300 mg per hari selama 8 hari tidak mengubah iloprost (zat aktif Ventavis) dalam tubuh.

Jika iloprost diberikan ke dalam pembuluh darah tidak berpengaruh pada digoxin (obat yang digunakan untuk mengobati gagal jantung dan irama jantung yang tidak normal) di dalam tubuh. Jika iloprost diberikan ke dalam pembuluh darah tidak berpengaruh pada obat yang disebut aktivator plasminogen tipe jaringan (t-PA, obat yang digunakan untuk melarutkan gumpalan darah) di dalam tubuh. Dalam sebuah penelitian pada hewan, ditemukan bahwa iloprost dapat mengakibatkan penurunan konsentrasi plasma kondisi mapan aktivator plasminogen tipe jaringan (t-PA).

Meskipun, studi klinis belum dilakukan, studi in vitro iloprost menunjukkan bahwa tidak ada penghambatan dari enzim sitokrom P450 (enzim yang mengambil bagian dalam metabolisme banyak obat) oleh iloprost (zat aktif Ventavis) yang diharapkan.

Harap beri tahu dokter atau apoteker Anda jika Anda sedang atau baru saja mengkonsumsi obat lain, termasuk obat yang diperoleh tanpa resep.

Mintalah saran dari dokter atau apoteker Anda sebelum minum obat apa pun. Dokter/apoteker anda memiliki lebih banyak informasi tentang obat-obatan yang harus diperhatikan atau dihindari saat menggunakan Ventavis.

Kehamilan

- **Jika Anda menderita hipertensi pulmonal,** hindari kehamilan karena kehamilan dapat memperburuk kondisi Anda dan bahkan dapat membahayakan hidup Anda.
- **Jika Anda berpotensi hamil,** gunakan kontrasepsi sejak Anda memulai pengobatan dan selama pengobatan.
- **Jika Anda sedang hamil, atau mungkin sedang hamil,** segera beri tahu dokter Anda. Ventavis hanya boleh digunakan selama kehamilan jika dokter Anda memutuskan bahwa potensi manfaatnya lebih besar daripada risikonya bagi Anda dan janin.

Menyusui

Anda tidak boleh menyusui selama perawatan dengan Ventavis karena tidak diketahui apakah Ventavis terserap ke dalam ASI.

Mengemudi atau menggunakan mesin

Anda harus berhati-hati pada awal terapi Ventavis. Ventavis menurunkan tekanan darah dan dapat menyebabkan pusing atau sakit kepala ringan pada beberapa orang. Jangan mengemudi atau mengoperasikan alat atau mesin apa pun jika Anda merasakan efek ini.

3. CARA MENGGUNAKAN VENTAVIS

Berapa banyak yang harus dihirup dan untuk berapa lama.

Selalu gunakan Ventavis seperti apa yang diperintahkan dokter Anda. Dosis Ventavis dan durasi pengobatan yang tepat untuk Anda tergantung pada kondisi Anda dan akan dilakukan oleh dokter Anda. Ventavis ditujukan untuk pengobatan jangka panjang.

Ventavis 10 mikrogram / mL digunakan dengan jenis nebulizer yang sesuai

Secara umum, saat memulai pengobatan Ventavis, dosis inhalasi pertama harus 2,5 mikrogram iloprost (seperti yang diberikan di corong). Jika dosis ini dapat ditoleransi dengan baik, dosis harus ditingkatkan menjadi 5 mikrogram dan dipertahankan pada dosis tersebut.

Dalam kasus toleransi yang buruk dari dosis 5 mikrogram, dosis harus dikurangi menjadi 2,5 mikrogram.

Kebanyakan orang akan memiliki 6 hingga 9 sesi inhalasi sepanjang hari. Satu sesi inhalasi biasanya akan berlangsung sekitar 4 sampai 10 menit tergantung pada dosis yang ditentukan dan pada nebulizer.

Jika Anda memiliki masalah ginjal atau hati

Tidak perlu adaptasi dosis pada **pasien dengan masalah ginjal ringan atau sedang** (pasien dengan klirens kreatinin > 30 mL/menit). Pasien dengan masalah ginjal yang parah (klirens kreatinin 30 mL/menit) tidak dilakukan investigasi dalam uji klinis dengan Ventavis.

Jika Anda memiliki masalah ginjal yang sangat parah dan memerlukan dialisis atau jika Anda memiliki masalah hati, dokter Anda akan memperkenalkan Ventavis kepada Anda secara bertahap dan mungkin meresepkan beberapa inhalasi setiap hari. Pada permulaan terapi, dosis 2,5 mikrogram harus digunakan dengan interval pemberian dosis 3 - 4 jam (disesuaikan dengan pemebrian maksimal 6 pemberian per hari). Setelah itu, dokter Anda mungkin dengan hati-hati memperpendek interval pemberian dosis tergantung pada bagaimana Anda menrespon pengobatan. Jika dokter Anda memutuskan untuk meningkatkan dosis hingga 5,0 mikrogram, interval dosis 3 - 4 jam harus dipilih sebagai pengobatan awal dan dipersingkat tergantung pada bagaimana Anda merespon pengobatan.

Cara menghirup

Cairan nebulizer Ventavis dihirup menggunakan alat khusus yang disebut nebulizer. Nebulizer mengubah cairan Ventavis menjadi kabut yang Anda hirup melalui mulut. Ikuti dengan seksama setiap instruksi yang disertakan dengan nebulizer. Tanyakan kepada dokter atau apoteker Anda jika Anda tidak yakin.

Untuk setiap sesi inhalasi Anda harus menggunakan ampul baru Ventavis. Tepat sebelum Anda mulai menghirup, pecahkan ampul kaca dan isi cairan ke dalam ruang obat nebulizer dengan mengikuti instruksi penggunaan nebulizer. Setiap cairan Ventavis yang tersisa di nebulizer setelah terhirup harus dibuang. Ikuti dengan seksama instruksi yang disertakan dengan nebulizer terutama instruksi tentang kebersihan dan pembersihan nebulizer.

Perhatian:

Saat Anda mulai menghirup Ventavis, dokter Anda akan memutuskan apakah terapi sebelumnya perlu disesuaikan (lihat juga bagian 'Apa yang perlu Anda ketahui sebelum menggunakan Ventavis/Penggunaan bersamaan obat lain').

Jangan biarkan cairan Ventavis bersentuhan dengan kulit atau mata Anda. Untuk inhalasi Anda harus menggunakan corong untuk menghindari Ventavis bersentuhan dengan kulit Anda. Jangan gunakan masker wajah. Jangan menelan cairan Ventavis, lihat bagian 'Berhati-hatilah menggunakan Ventavis'.

Pastikan ventilasi atau sirkulasi udara pada ruangan di mana Anda melakukan pengobatan Ventavis. Orang lain mungkin secara tidak sengaja terpapar Ventavis melalui udara ruangan. Jika Anda mulai menggunakan nebulizer baru, Anda akan didampingi oleh dokter Anda.

Dokter Anda akan memberi Anda nebulizer yang cocok untuk menghirup cairan nebulizer Ventavis 10 mikrogram / mL Anda. Bicaralah dengan dokter Anda.

Jika Anda menggunakan lebih banyak Ventavis daripada yang seharusnya
Menggunakan lebih banyak Ventavis daripada yang seharusnya dapat menyebabkan pusing, sakit kepala, muka memerah (wajah memerah), mual (merasa sakit), sakit rahang atau sakit punggung. Anda juga mungkin mengalami penurunan atau peningkatan tekanan darah, bradikardia (berkurangnya denyut jantung), takikardia (peningkatan denyut jantung), muntah, diare atau nyeri tungkai.

Jika salah satu dari ini terjadi:

- Hentikan sesi inhalasi.
- Bicaralah dengan dokter Anda.

Dokter Anda akan memantau Anda dan mengobati gejala yang timbul. Antidot spesifik tidak diketahui.

Jika Anda lupa menggunakan Ventavis

Jangan menggunakan dosis ganda untuk mengganti dosis yang terlupakan. Silakan tanyakan kepada dokter Anda apa yang harus Anda lakukan.

Jika Anda berhenti menggunakan Ventavis

Jika Anda berhenti atau ingin menghentikan pengobatan, Anda harus membicarakan hal ini dengan dokter Anda terlebih dahulu. Jika Anda memiliki pertanyaan lebih lanjut tentang penggunaan produk ini, tanyakan kepada dokter atau apoteker Anda

4. KEMUNGKINAN EFEK SAMPING

Seperti semua obat-obatan, Ventavis dapat menyebabkan efek samping, meskipun tidak semua orang mendapatkannya.

Efek samping yang paling sering diamati pada pasien yang menerima Ventavis (dapat terjadi 20 atau lebih, pada 100 pasien) termasuk vasodilatasi (pelebaran pembuluh darah), sakit kepala dan batuk.

Efek samping yang paling serius (efek samping yang berakibat fatal atau mengancam jiwa telah diobservasi) pada pasien yang menerima Ventavis adalah hipotensi (tekanan darah rendah), kejadian perdarahan, dan bronkospasme (penyempitan saluran udara dengan kemungkinan kesulitan bernapas).

Di bawah ini daftar kemungkinan efek samping berdasarkan frekuensi kejadian efek samping.

Sangat umum (terjadi lebih dari pada 1 dari 10 orang)

- kejadian perdarahan (kebanyakan epistaksis (mimisan) dan hemoptisis (batuk darah dari saluran pernapasan) sangat umum, terutama jika Anda juga minum obat pengencer darah (antikoagulan). Risiko perdarahan dapat meningkat bila inhibitor agregasi trombosit atau antikoagulan diberikan secara bersamaan (lihat juga bagian 'Apa yang perlu Anda ketahui sebelum menggunakan Ventavis/Penggunaan bersamaan obat lain') Kasus fatal perdarahan otak dan intrakranial (pendarahan di otak) telah dilaporkan.
- sakit kepala
- vasodilatasi (pelebaran pembuluh darah; gejala dapat berupa kemerahan atau kemerahan pada wajah)
- nyeri dada
- batuk
- mual
- trismus (nyeri pada rahang/kejang otot rahang)
- edema perifer (pembengkakan yang meluas, biasanya pada tungkai bawah)

Umum (terjadi hingga pada 1 dari 10 orang)

- hipotensi (tekanan darah rendah)
- takikardia (detak jantung cepat)
- palpitasi (kesadaran detak jantung cepat atau keras)
- sinkop (pingsan); sinkop adalah gejala umum dari penyakit itu sendiri tetapi juga dapat terjadi dikarenakan terapi pengobatan. Lihat juga bagian 'Berhati-hatilah menggunakan Ventavis' untuk saran tentang apa yang dapat Anda lakukan dan hindari.
- dispnea (kesulitan bernapas)
- pusing

- nyeri faringolaryngeal (nyeri saat menelan)
- iritasi tenggorokan
- diare
- muntah
- iritasi mulut dan lidah termasuk nyeri
- ruam
- nyeri punggung

Tidak diketahui (frekuensi tidak dapat diestimasi dari data yang tersedia)

- bronkospasme (penyempitan saluran napas dengan kemungkinan kesulitan bernapas) dan mengi (lihat juga bagian bagian 'Berhati-hatilah menggunakan Ventavis')
- hipersensitivitas (yaitu alergi)
- trombositopenia (penurunan jumlah trombosit darah)
- hidung tersumbat (hidung tersumbat)
- dysgeusia (gangguan indera perasa)

Jika Anda merasakan efek samping, bicarakan dengan dokter atau apoteker Anda. Termasuk juga kemungkinan efek samping yang tidak tercantum dalam selebaran ini.

Pelaporan dugaan efek samping obat

Jika mengalami efek samping selama dan/atau setelah penggunaan obat, segera konsultasikan ke dokter atau tenaga kesehatan lainnya.

Untuk pelaporan efek samping, silahkan email ke drugsafety.indonesia@bayer.com. Informasi yang disampaikan sangat penting untuk pemantauan manfaat-risiko produk yang berkelanjutan.

5. CARA MENYIMPAN VENTAVIS

Jauhkan dari pandangan dan jangkauan anak-anak.

Jangan gunakan Ventavis setelah tanggal kedaluwarsa yang tertera pada kemasan.

Produk obat ini tidak memerlukan kondisi penyimpanan khusus.

6. KEMASAN DAN INFORMASI LAINNYA

Apa kandungan Ventavis

- **Zat aktifnya** adalah iloprost (sebagai iloprost trometamol).
- **Bahan lainnya** adalah trometamol, etanol, natrium klorida, asam hidroklorida (untuk penyesuaian pH) dan air untuk injeksi.

Ventavis 10 mikrogram / mL :

1 mL cairan nebulizer mengandung 10 mikrogram iloprost (sebagai iloprost trometamol).

Satu ampul dengan 2 mL cairan nebulizer mengandung 20 mikrogram iloprost (sebagai iloprost trometamol).

Seperti apa Ventavis dan isi kemasannya

Ventavis adalah cairan steril yang jernih dan tidak berwarna untuk dihirup.

Kemasan : Dus, 30 ampul @ 2 ml

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