Applicant: Accord Healthcare (Pty) Ltd	

FINAL PROFESSIONAL PACKAGE INSERT
18.07.2020

1.3.1.1 PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

MIANDA 25 mg (Powder for concentrate for solution for infusion)

MIANDA 100 mg (Powder for concentrate for solution for infusion)

Strength:

MIANDA 25 mg: Each 10 ml vial contains 25 mg bendamustine hydrochloride.

MIANDA 100 mg: Each 50 ml vial contains 100 mg bendamustine hydrochloride.

Pharmaceutical form:

Powder for concentrate for solution for infusion

White, microcrystalline powder

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Qualitative declaration:

Bendamustine hydrochloride.

Quantitative composition

1 ml of the concentrate contains 2,5 mg bendamustine hydrochloride when reconstituted according to Instructions for use.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion.

White, microcrystalline powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- First-line treatment of chronic lymphocytic leukaemia (Binet stage B or C) in patients for whom fludarabine combination chemotherapy is not appropriate.
- First-line treatment of indolent CD 20 positive non-Hodgkin's lymphoma in combination with rituximab.
- Indolent non-Hodgkin's lymphomas as monotherapy in patients, who have progressed during or within 6 months following treatment with rituximab or a rituximab containing regimen.
- Front line treatment of multiple myeloma (Durie-Salmon stage II with progress or stage III) in combination with prednisone for patients older than 65 years who are not eligible for autologous stem cell transplantation and who have clinical neuropathy at time of diagnosis precluding the use of thalidomide or bortezomib containing treatment.

4.2 Posology and method of administration:

Posology

Monotherapy for chronic lymphocytic leukaemia

100 mg/m^2 body surface area **MIANDA** on days 1 and 2; every 4 weeks.

Combination treatment for first-line indolent non-Hodgkin's lymphoma

90 mg/m^2 body surface area **MIANDA** on days 1 and 2 in combination with 375 mg/m^2 body surface area rituximab as a slow I.V. infusion on day 1; every 4 weeks.

Monotherapy for indolent non-Hodgkin's lymphomas refractory to rituximab

120 mg/m^2 body surface area **MIANDA** on days 1 and 2; every 3 weeks.

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Multiple Myeloma

120-150 mg/m^2 body surface area **MIANDA** on days 1 and 2, 60 mg/m^2 body surface area prednisone I.V. or orally on days 1 to 4; every 4 weeks.

Hepatic impairment

On the basis of pharmacokinetic data, no dose adjustment is necessary in patients with mild hepatic impairment [serum bilirubin < 2 mg/dl (34,2 µmol/l)].

A 30 % dose reduction is recommended in patients with moderate hepatic impairment (serum bilirubin [2 – 3,0 mg/dl (34,2 µmol/l – 51,3 µmol/l)].

No data is available in patients with severe hepatic impairment [serum bilirubin values of > 3,0 mg/dl (51,3 µmol/l)].

Renal impairment

On the basis of pharmacokinetic data, no dose adjustment is necessary in patients with a creatinine clearance of > 10 ml/min. Experience in patients with severe renal impairment is limited.

Paediatric patients

There is no experience in children and adolescents with **MIANDA**.

Elderly patients

There is no evidence that dose adjustments are necessary in elderly patients (see section 5.2).

Method of administration:

Precautions to be taken before manipulation or handling medicine

When handling **MIANDA**, inhalation, skin contact or contact with mucous membranes should be avoided (wear gloves and protective clothes). Contaminated body parts should be carefully rinsed with water and soap, the eye should be rinsed with physiological saline solution.

If possible it is recommended to work on special safety workbenches (laminar flow) with liquid impermeable, absorbing disposable foil. Pregnant personnel should be excluded from handling cytostatics.

For instructions on reconstitution of the medicine (see section 6.6)

MIANDA is given via intravenous infusion over 30 to 60 minutes.
Infusion must be administered under the supervision of a medical practitioner qualified and experienced in the use of chemotherapeutic agents.

Poor bone marrow function is related to increased chemotherapy-induced haemotological toxicity. Treatment should not be started if leukocyte and/or platelet values dropped to < 3 x 10^9/l or < 75 x 10^9/l, respectively (see section 4.3).

Treatment should be terminated or delayed if leukocyte and/or platelet values dropped to ≤ 3 x 10^9/l or ≤ 75 x 10^9/l, respectively. Treatment can be continued after leukocyte values have increased to > 4 x 10^9/l and platelet values to > 100 x 10^9/l.

The leukocyte and platelet Nadir is reached, after 14 - 20 days with regeneration after 3 – 5 weeks. During therapy free intervals strict monitoring of the blood count is recommended (see section 4.4).

In case of non-haematological toxicity dose reductions have to be based on the worst CTC grades in the preceding cycle. A 50 % dose reduction is recommended in case of CTC grade 3 toxicity.

An interruption of treatment is recommended in case of CTC grade 4 toxicity. If a patient requires a dose modification the individually calculated reduced dose must be given on day 1 and 2 of the respective treatment cycle.

4.3 Contraindications:

- Hypersensitivity to the active substance or to any of the excipients in **MIANDA**
- Pregnancy and lactation

- Severe hepatic impairment [serum bilirubin > 2,0 mg/dl (34,2 µmol/l)]
- Jaundice
- Severe bone marrow suppression and severe blood count alterations (leukocyte and/or platelet values dropped to < 3 x 10^9/l or < 75 x 10^9/l, respectively)
- Major surgery less than 30 days before start of treatment
- Infections, especially involving leukocytopenia
- Yellow fever vaccination or any other live attenuated vaccine
- Congenital QT prolongation
- Concomitant medicines causing QT prolongation

4.4. Special warnings and precautions for use

Myelosuppression

Patients treated with **MIANDA** may experience myelosuppression. Treatment-related myelosuppression, leukocytes, platelets, haemoglobin, and neutrophils must be monitored at least weekly. Prior to the initiation of the next cycle of therapy, the following parameters are recommended: Leukocyte and/or platelet values > 4 x 10^9/l or > 100 x 10^9/l, respectively.

Infections

Serious infection, including pneumonia and sepsis, has been reported with bendamustine hydrochloride. Infection has been associated with hospitalisation, septic shock and death. Patients with neutropenia and/or lymphopenia following treatment with **MIANDA** are more susceptible to opportunistic infections. Opportunistic infection such as Pneumocystis jivovecii pneumonia (PJP), varicella zoster virus and cytomegalovirus (CMV) have been reported. Treatment with bendamustine hydrochloride may cause prolonged lymphocytopenia (<600/µl) and low CD4-positive T-cell (T-helper cell) counts (<200/µl) for atleast 7-9 months after the completion of treatment. Lymphocytopenia and

CD4-positive T-cell depletion are more pronounced when bendamustine is combined with rituximab. In case of low CD4-positive T-cell counts (<200/µl) Pneumocystis jirovecii pneumonia (PJP) prophylaxis should be considered. Cases of tuberculosis have been less frequently reported compared to other infections. Latent or dormant tuberculosis may become active (see section 4.8).

Patients with myelosuppression following **MIANDA** treatment should be advised to contact a medical practitioner if they have symptoms or signs of infection, including fever or respiratory symptoms. Discontinuation of bendamustine hydrochloride should be considered if there are signs of (opportunistic) infections. The presence of tuberculosis should be excluded before treatment with **MIANDA** is commenced.

Hepatitis B reactivation

Reactivation of hepatitis B in patients who are chronic carriers of this virus has occurred after these patients received bendamustine hydrochloride. Some cases resulted in acute hepatic failure or a fatal outcome. Patients should be tested for HBV infection before initiating treatment with bendamustine hydrochloride. Experts in liver disease and in the treatment of hepatitis B should be consulted before treatment is initiated in patients with positive hepatitis B tests (including those with active disease) and for patients who test positive for HBV infection during treatment. Carriers of HBV who require treatment with bendamustine hydrochloride should be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy (see section 4.8).

Skin reactions

A number of skin reactions have been reported. These events have included rash, severe skin reactions and bullous exanthema. Cases of Stevens-Johnson syndrome (SJS), and Toxic Epidermal Necrolysis (TEN) and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), some fatal,

have been reported with the use of bendamustine hydrochloride (see section 4.8). Patients should be advised of the signs and symptoms of these reactions by their prescribers and should be told to seek medical attention immediately if they develop these symptoms. Some of these events occurred when bendamustine hydrochloride was given in combination with other anticancer agents.

Where skin reactions occur, they may be progressive and increase in severity with further treatment. If skin reactions are progressive, **MIANDA** should be withheld or discontinued. For severe skin reactions where a relationship to **MIANDA** is suspected, treatment should be discontinued.

Cardiac disorders

During treatment with **MIANDA** the concentration of potassium in the blood must be closely monitored. When serum potassium levels are < 3,5 mEq/l, (3,5 mmol/l) an ECG measurement must be performed and potassium supplement must be given. Fatal cases of myocardial infarction and cardia failure have been reported with bendamustine hydrochloride treatment. Patients with concurrent or history of cardiac disease should be observed closely.

Nausea, vomiting

An antiemetic should be given for the symptomatic treatment of nausea and vomiting.

Tumour lysis syndrome

Tumour lysis syndrome associated with bendamustine hydrochloride treatment has been reported in patients in clinical trials. The onset tends to be within 48 hours of the first dose of bendamustine hydrochloride and, without intervention, may lead to acute renal failure and death. Preventive measures include adequate volume status and close monitoring of blood chemistry, particularly potassium and uric acid levels.

The use of allopurinol during the first one to two weeks of **MIANDA** therapy can be considered. However, there have been a few cases of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis reported when bendamustine hydrochloride and allopurinol are administered concomitantly.

Anaphylaxis

Infusion reactions to bendamustine hydrochloride have occurred commonly in clinical trials. Symptoms include fever, chills, pruritus and rash. Severe anaphylactic and anaphylactoid reactions have occurred. Patients must be asked about symptoms suggestive of infusion reactions after their first cycle of therapy.

Measures to prevent severe reactions, including antihistamines, antipyretics and corticosteroids must be considered in subsequent cycles in patients who have previously experienced infusion reactions.

In patients who experienced Grade 3 or worse allergic-type reactions, **MIANDA** should be discontinued.

Contraception

Bendamutine hydrochloride is teratogenic and mutagenic.

Women should not become pregnant during treatment. Male patients should not father a child during and up to 6 months after treatment. They should seek advice about sperm conservation prior to treatment with **MIANDA** because of possible irreversible infertility.

Extravasation

An extravasal injection should be stopped immediately. The needle should be removed after a short aspiration. Thereafter the affected area of tissue should be cooled. The arm should be elevated. Additional treatments like the use of corticosteroids are not of clear benefit.

There have been reports of necrosis after accidental extra-vascular administration and toxic epidermal necrosis, tumour lysis syndrome, and anaphylaxis. (see section 4.8).

There are reports of secondary tumours, including myelodysplastic syndrome, myeloproliferative disorders, acute myeloid leukaemia and bronchial carcinoma.

4.5 Interaction with other medicines and other forms of interaction

No *in-vivo* interaction studies have been performed.

When **MIANDA** is combined with myelosuppressive agents, the effect of **MIANDA** and/or the co-administered medicinal products on the bone marrow may be potentiated. Any treatment reducing the patient's performance status or impairing bone marrow function can increase the toxicity of **MIANDA**.

Combination of **MIANDA** with ciclosporin or tacrolimus may result in excessive immunosuppression with risk of lymphoproliferation.

Cytostatics can reduce antibody formation following live-virus vaccination and increase the risk of infection which may lead to fatal outcome. This risk is increased in subjects who are already immunosuppressed by their underlying disease.

Bendamustine hydrochloride metabolism involves cytochrome P450 (CYP) 1A2 isoenzyme. Therefore, potential for interaction with CYP1A2 inhibitors such as fluvoxamine, ciprofloxacin, acyclovir, and cimetidine exists.

4.6 Fertility, Pregnancy and lactation

Pregnancy

There are no adequate data from the use of **MIANDA** in pregnant women.

In nonclinical studies bendamustine hydrochloride was embryo/fetolethal, teratogenic and genotoxic. Therefore, **MIANDA** is contraindicated during pregnancy (see section 4.3).

Women of childbearing potential/contraception

Women of childbearing potential must use effective methods of contraception both before and during **MIANDA** therapy.

Breast-feeding

It is not known whether bendamustine passes into the breast milk, therefore it is contraindicated during breast-feeding (see section 4.3). Breast-feeding must be discontinued during treatment with **MIANDA**.

Fertility

Men being treated with **MIANDA** are advised not to father a child during and for up to 6 months

following cessation of treatment. Advice on conservation of sperm should be sought prior to treatment because of the possibility of irreversible infertility due to therapy with **MIANDA**.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, ataxia, peripheral neuropathy and somnolence have been reported during treatment with bendamustine hydrochloride (see section 4.8). Patients should be instructed that if they experience these symptoms they should avoid potentially hazardous tasks such as driving and using machines.

4.8 Undesirable effects

The most frequent side effects with **MIANDA** are haematological adverse reactions (leukopenia, thrombocytopenia), dermatologic toxicities (allergic reactions), constitutional symptoms (fever), gastrointestinal symptoms (nausea, vomiting).

Infections and infestations:

Frequent: Infection (not otherwise specified), opportunistic infection (including Herpes zoster, cytomegalovirus, hepatitis B)

Less frequent: Pneumocystis jiroveci pneumonia, septicaemia, primary atypical pneumonia, tuberculosis (TB)

Neoplasms benign and malignant:

Frequent: Tumour lysis syndrome

Less frequent: Myelodysplastic syndrome, acute myeloid leukaemia

Blood and lymphatic system disorders:

Frequent: Leukopenia (not otherwise specified), thrombocytopenia, haemorrhage, anaemia, neutropenia, lymphopenia

Less frequent: Pancytopenia, bone marrow failure, haemolysis

Immune system disorders:

Frequent: Hypersensitivity (not otherwise specified)

Less frequent: Anaphylactic reaction, anaphylactoid reaction, anaphylactic shock

Metabolism and nutrition disorders:

Frequent: Tumour lysis syndrome

Nervous system disorders:

Frequent: Headache, insomnia, dizziness

Less frequent: Somnolence, aphonia, dysgeusia, paraesthesia, peripheral sensory neuropathy, anticholinergic syndrome, neurological disorders, ataxia, encephalitis

Cardiac disorders:

Frequent: Cardiac dysfunction, such as, palpitations, angina pectoris, dysrhythmia

Less frequent: Pericardial effusion, tachycardia, myocardial infarction, cardiac failure,

Frequency unknown: Atrial fibrillation

Vascular disorders:

Frequent: Hypotension, hypertension

Less frequent: Acute circulatory failure, phlebitis

Respiratory, thoracic and mediastinal disorders:

Frequent: Pulmonary dysfunction

Less frequent: Pulmonary fibrosis

Frequency unknown: Pneumonitis, pulmonary alveolar haemorrhage

Gastrointestinal disorders:

Frequent: Nausea, vomiting, diarrhoea, constipation, stomatitis

Less frequent: Haemorrhagic oesophagitis, gastrointestinal haemorrhage

Hepato-biliary disorders:

Frequency unknown: Hepatic failure

Skin and subcutaneous tissue disorders:

Frequent: Alopecia, skin disorders (not otherwise specified)

Less frequent: Erythema, dermatitis, pruritus, maculopapular rash, hyperhidrosis

Frequency unknown: Stevens – Johnson syndrome, Toxic Epidermal Necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS)*

Renal and urinary disorders:

Frequency unknown: Renal failure

Reproductive system and breast disorders:

Frequent: Amenorrhoea

Less frequent: Infertility

General disorders and administration site conditions

Frequent: Mucosal inflammation, fatigue, pyrexia, pain, chills, dehydration, anorexia

Less frequent: Multi organ failure

Investigations

Frequent: Haemoglobin decrease, creatinine increase, urea increase, AST increase, ALT increase, alkaline phosphatase increase, bilirubin increase, hypokalaemia.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

After application of a 30 min infusion of bendamustine once every 3 weeks the maximum tolerated dose (MTD) was 280 mg/m^2. Cardiac events of CTC grade 2 which were compatible with ischaemic ECG changes occurred which were regarded as dose limiting.

In a subsequent study with a 30 min infusion of bendamustine at day 1 and 2 every 3 weeks the MTD was found to be 180 mg/m^2. The dose limiting toxicity was grade 4, thrombocytopenia. Cardiac toxicity was not dose limiting with this schedule.

Counter measures

There is no specific antidote. Bone marrow transplantation and transfusions (platelets, concentrated erythrocytes) may be made or haematological growth factors may be given as effective countermeasures to control haematological side effects.

Bendamustine and its metabolites are dialyzable to a small extent.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties:

Pharmacotherapeutic group: Antineoplastic agents, alkylating agents,

ATC code: L01AA09

Bendamustine hydrochloride is an alkylating antitumor agent. The antineoplastic and cytocidal effect of bendamustine hydrochloride is based essentially on a cross linking of DNA single and double strands by alkylation. As a result, DNA matrix functions and DNA synthesis and repair are impaired.

The antitumor effect of bendamustine hydrochloride has been demonstrated by several *in-vitro* studies in different human tumour cell lines (breast cancer, non-small cell and small cell lung cancer, ovarian carcinoma and various leukaemia) and *in-vivo* in different experimental tumour models with tumours of mouse, rat and human origin (melanoma, breast cancer, sarcoma, lymphoma, leukaemia and small cell lung cancer).

The active substance revealed no or very low cross-resistance in human tumour cell lines with different resistance mechanisms at least in part due to a comparatively persistent DNA interaction. Additionally, it was shown in clinical studies that there is no complete cross-resistance of bendamustine with anthracyclines, alkylating agents or rituximab. However, the number of assessed patients is small.

5.2 Pharmacokinetic properties

Distribution

The elimination half-life $t_{1/2ß}$ after 30 min I.V. infusion of 120 mg/m^2 area to 12 subjects was 28,2 minutes. Following 30 min I.V. infusion the central volume of distribution was 19,3 litre. Under steady-state conditions following I.V. bolus injection the volume of distribution was 15,8 – 20,5 l.

More than 95 % of the substance is bound to plasma proteins (primarily albumin).

Metabolism

A major route of clearance of bendamustine is the hydrolysis to monohydroxy- and dihydroxy-bendamustine. Formation of N-desmethyl-bendamustine and gamma-hydroxy bendamustine by hepatic metabolism involves cytochrome P450 (CYP) 1A2 isoenzyme. Another major route of bendamustine metabolism involves conjugation with glutathione.

In-vitro bendamustine does not inhibit CYP 1A4, CYP 2C9/10, CYP 2D6, CYP 2E1 and CYP 3A4.

Elimination

The mean total clearance after 30 min I.V. infusion of 120 mg/m^2 body surface area to 12 subjects was 639,4 ml/minute.

About 20 % of the administered dose was recovered in urine within 24 hours. Amounts excreted in urine were in the order monohydroxy-bendamustine > bendamustine > dihydroxy-bendamustine > oxidised metabolite > N-desmethyl bendamustine. In the bile, primarily polar metabolites are eliminated.

Hepatic impairment

In patients with 30 to 70 % tumour infestation of the liver and mild or moderate hepatic impairment [serum bilirubin < 2,0 mg/dl (34,2 µmol/l)] the pharmacokinetic behaviour was not changed.

There was no significant difference to patients with normal liver and kidney function with respect to C_{max}, t_{max}, AUC, $t_{1/2ß}$, volume of distribution and clearance. AUC and total body clearance of bendamustine correlate inversely with serum bilirubin.

Renal impairment

In patients with creatinine clearance > 10 ml/min including dialysis dependent patients, no significant difference to patients with normal liver and kidney function was observed with respect to C_{max}, t_{max}, AUC, $t_{1/2ß}$, volume of distribution and clearance.

Elderly subjects

Subjects up to 84 years of age were included in pharmacokinetic studies. Higher age does not influence the pharmacokinetics of bendamustine.

5.3 Preclinical safety data

Not applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol

6.2 Incompatibilities

MIANDA must not be mixed with other medicinal products except those mentioned in section 4.2~~,~~ (Instructions for use).

6.3 Shelf life

3 years.

Reconstituted concentrate:

The powder should be reconstituted immediately after opening of the vial.

The reconstituted concentrate should be diluted immediately with 0,9 % sodium chloride solution.

Solution for infusion:

After reconstitution and dilution, chemical and physical stability has been demonstrated for 3.5 hours at 25 °C and 2 days at 2 °C to 8 °C in polyethylene bags.

From a microbiological point of view, the solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

6.4 Special precautions for storage

Store below 25 °C.

Keep the vial in the outer carton to protect from light.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

Identification

A white to off white lyophilised cake or powder in an amber glass vial.

Presentation

MIANDA 25 mg is packed in a 10 ml dark, amber tubular Type I glass vial, with a grey rubber stopper and sealed with a 20 mm blue aluminium seal.

MIANDA 100 mg is packed in a 50 ml dark, amber tubular Type I glass vial, with a grey rubber stopper and sealed with a 20 mm blue aluminium seal.

6.6 Special precautions for disposal and other handling

When handling **MIANDA**, inhalation, skin contact or contact with mucous membranes should be avoided (wear gloves and protective clothes!). Contaminated body parts should be carefully rinsed with water and soap, the eye should be rinsed with physiological saline solution. If possible it is recommended to work on special safety workbenches (laminar flow) with liquid impermeable, absorbent disposable foil. Pregnant personnel should be excluded from handling cytostatics. (see section 4.2).

The powder for concentrate for solution for infusion has to be reconstituted with water for injection, diluted with sodium chloride 9 mg/ml (0,9 %) solution for injection and then administered by intravenous infusion. Aseptic technique is to be used (see section 4.2 Instructions for use).

The powder for concentrate for solution for infusion has to be reconstituted with water for injection, diluted with sodium chloride 9 mg/ml (0,9 %) solution for injection and then administered by intravenous infusion. Aseptic technique is to be used.

1. Reconstitution

- Reconstitute each
- vial of **MIANDA** containing 25 mg bendamustine hydrochloride in 10 ml water for injection by shaking.

Reconstitute each vial of **MIANDA** containing 100 mg bendamustine hydrochloride in 40 ml water for injection by shaking.

The reconstituted concentrate contains 2,5 mg bendamustine hydrochloride per ml and appears as a clear colourless solution.

2. Dilution

As soon as a clear solution is obtained (usually after 5-10 minutes) dilute the total recommended dose of **MIANDA** immediately with 0,9 % NaCl solution to produce a final volume of about 500 ml.

MIANDA must be diluted with 0,9 % NaCl solution and not with any other injectable solution.

3. Administration

The solution is administered by intravenous infusion over 30 - 60 min.

The vials are for single use only.

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

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7. HOLDER OF CERTIFICATE OF REGISTRATION

Accord Healthcare (Pty) Ltd.,

Tuscany Office Park,

6 Coombe Place,

Rivonia,

Gauteng,

South Africa

8. REGISTRATION NUMBER

MIANDA 25: 52/26/0433

MIANDA 100: 52/26/0434

9. DATE OF PUBLICATION OF THIS PACKAGE INSERT:

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