SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

V-DALGIN CONCENTRATED SYRUP FOR ADULTS

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml contains 250 mg Dipyrone.

Excipients with known effect:

Each 1 ml contains 20.7 mg sodium and 166.7 mg sucrose (see section 4.4).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral syrup, yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Relief of moderate to severe pain as in headache, toothache, dysmenorrhea and for high fever that does not respond to other measures.

4.2 Posology and method of administration

Posology

The dosage depends on the intensity of pain or fever and the individual sensitivity to react to **V-DALGIN CONCENTRATED SYRUP FOR ADULTS**. It is important that the lowest dose controlling pain and fever is selected.

Recommended dosage:

Adults and adolescence above 15 years of age (over 53 kg body weight):

2 to 4 ml as needed up to 3 times a day.

The medicine should be taken at intervals of 6-8 hours.

Do not take more than 3 doses in 24 hours.

This medicine is not intended for children under 15 years of age.

Do not exceed the recommended dose.

Duration of use

The duration of use depends on type and severity of the disease. If the fever lasts more than 3 days or pain persists more than 7 days despite the treatment, the patient should contact a doctor.

Method of administration

For oral administration. This medical product should be taken with a glass of water, before or after a meal.

4.3 Contraindications

- Hypersensitivity to the active substance Dipyrone or other pyrazolones or pyrazolidines, or to any of the excipients listed in section 6.1.
- Agranulocytosis in the medical history induced by metamizole, other pyrazolones or pyrazolidines.
- Patients with known analgesic asthma syndrome or known analgesic intolerance of the urticaria-angioedema type, i.e. patients who show bronchospasm or other anaphylactoid forms of reaction (e.g. urticaria, rhinitis, angioedema) to salicylates, paracetamol or other non-narcotic analgesics such as diclofenac, ibuprofen, indomethacin or naproxen.
- Impaired bone marrow function or diseases of the hematopoietic system
- Genetically induced glucose-6 phosphate dehydrogenase (G6PD) deficiency (hemolysis risk).
- Acute intermittent hepatic porphyria (risk of triggering a porphyria attack).
- Third trimester of pregnancy.

4.4 Special warnings and precautions for use

V-DALGIN CONCENTRATED SYRUP FOR ADULTS contains the pyrazolone derivative Dipyrone and bears the rare, but life-threatening risks of shock and agranulocytosis (see section 4.8).

Patients showing anaphylactoid reactions to this medical product are particularly at risk to react similarly to other non-narcotic analgesics.

Patients showing an anaphylactic or another immunologically mediated reaction to this medical product (e.g. agranulocytosis), are particularly at risk to react similarly to other pyrazolones and pyrazolidines medical products.

Patients showing an anaphylactic or other immunologically mediated reaction to other pyrazolones, pyrazolidines or other non-narcotic analgesics medical products, are also at high risk to react correspondingly to this medical product.

Agranulocytosis

Treatment with metamizole can cause agranulocytosis, which may be fatal (see section 4.8). It may occur even after metamizole has previously been used without complications.

Metamizole-induced agranulocytosis is an idiosyncratic adverse reaction. It is not dose-dependent, and may occur at any time during treatment, even shortly after treatment discontinuation.

Patients must be instructed to discontinue their treatment and seek immediate medical attention in case any symptoms suggestive of agranulocytosis appear (e.g. fever, chills, sore throat and painful mucosal changes, especially in the mouth, nose and throat or in the genital or anal region).

If metamizole is taken for fever, some symptoms of emerging agranulocytosis may go unnoticed. Similarly, symptoms may also be masked in patients receiving antibiotic therapy.

If signs and symptoms suggestive of agranulocytosis occur, a complete blood cell count (including different blood count) should be performed immediately, and treatment must be stopped while waiting for the results. If confirmed, treatment must not be reintroduced (see section 4.8).

Thrombocytopenia

If signs of thrombocytopenia, such as increased tendency to bleeding and petechiae on the skin and mucosal membranes, occur (see section 4.8), the use of this medical product must be stopped and the blood count (including differential blood count) must be checked immediately. Discontinuation of treatment must not be deferred until the results of the laboratory tests are available.

Pancytopenia

In the event of pancytopenia, treatment must be discontinued immediately, and the full blood count must be monitored until it has normalized (see section 4.8). All patients should be informed that they should immediately see a physician if signs of disease and symptoms occur during treatment, which indicate blood dyscrasia (e.g. general malaise, infection, persistent fever, effusions, bleeding, paleness).

Anaphylactic/anaphylactoid reactions

When selecting the method of application, please consider that the parenteral administration of this medical product is associated with a higher risk for anaphylactic or anaphylactoid reactions.

The risk of potentially severe anaphylactoid reactions to this medical product is obviously increased in patients with:

- Analgesic asthma syndrome or analgesic intolerance of the urticaria-angioedema type (see section 4.3).
- Bronchial asthma, in particular with simultaneously existing rhinosinusitis and nasal polyps,
- chronic urticaria.
- Alcohol intolerance. Such patients react already to small quantities of alcoholic beverages with symptoms such as sneezing, watering eyes and severe facial reddening. Such an alcohol intolerance might be an indication of an analgesic asthma syndrome not yet diagnosed to date (see section 4.3).

An anaphylactic shock may predominantly occur in sensitive patients. Therefore, particular caution should be taken for the use in patients with asthma or atopy.

The patient must be asked accordingly before the administration of this medical product. In patients with an increased risk for anaphylactoid reactions, this medical product must only be used following careful weighing of possible risk against the expected benefits (see also section 4.3). If this medical product is administered in such cases, the patient must be monitored at close intervals by a physician and readiness for cases of emergency must be ensured.

Severe cutaneous reactions

Severe cutaneous skin reactions (SCARs), including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS), which might be life-threatening or fatal, were reported in connection with Dipyrone treatment.

The patients must be informed about the signs and symptoms and be monitored closely for skin reactions.

If signs and symptoms occur that indicate these reactions, Dipyrone should be discontinued immediately and treatment with Dipyrone must at no point be resumed (see section 4.3).

Drug-induced liver damage

Cases of hepatitis, which had a predominantly a hepatocellular pattern and which occurred within a few days up to a few months after the start of treatment, were reported in patients who were treated

with Dipyrone. Signs and symptoms included increased liver enzyme values in serum with or without jaundice, often in connection with other drug hypersensitivity reactions (e.g. rash, changes in the blood count, fever and eosinophilia) or accompanied by features of autoimmune hepatitis. Most patients recovered after discontinuation of Dipyrone treatment. In individual cases, however, a progression to acute liver failure with need for liver transplantation was reported.

The mechanism of Dipyrone-induced liver damage is not clearly understood. The data, however, reveal indications of an immune-allergic mechanism.

Patients should be asked to contact their doctor if symptoms occur which indicate liver damage. In these patients, treatment with Dipyrone should be discontinued and the liver function should be checked.

Dipyrone should not be used again in a liver damage, for which no other cause could be found, occurred previously with Dipyrone treatment.

Isolated hypotensive reactions

This medical product might trigger hypotensive reactions (see also section 4.8). These reactions might depend on the dose. This is more likely with parenteral than with enteral administration.

The risk of such reactions is also increased in:

- Patients with, for example, previous hypotension, volume deficiency or dehydration, unstable circulation or incipient circulation failure (such as in patients with myocardial infarction or polytrauma).
- Patients with high fever.

Careful verification of the indication and monitoring at close intervals are therefore necessary in these patients. Preventative measures (such as stabilization of circulation) might be required to reduce the risk of hypotensive reactions.

This medical product must only be used with careful monitoring of the hemodynamic parameters in patients in whom a lowering of the blood pressure must be avoided under all circumstances, such as patients with severe coronary heart disease or relevant stenoses of the vessels supplying the brain.

This medical product should only be used following strict risk-benefit assessment and respective precautionary measures in elderly patients and patients with impaired kidney and liver function.

Children and adolescents:

This medical product is not intended for children under 15 years of age.

Excipients:

- Sodium:
  This medicinal product contains 41.38 mg sodium per unit dose of 2 ml, equivalent to 2% of the maximum daily dietary sodium intake of 2 g, recommended by the World Health Organization (WHO) for an adult.
- Sucrose:
  This medicinal product contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicinal product.
  Additionally, teeth damage (caries) may occor only when the medical product is intended for chronic use, e.g. for two weeks or more.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic induction of metabolizing enzymes:

Dipyrone might induce metabolizing enzymes, including CYP2B6 and CYP3A4. The simultaneous use of Dipyrone with bupropion, efavirenz, methadone, valproate, ciclosporin, tacrolimus or sertraline might result in a reduction of the plasma concentration of these

medicinal products with a potential decrease in clinical efficacy. Therefore, caution must be taken when using Dipyrone simultaneously with these drugs; the clinical response and/or the efficacy levels should be monitored accordingly.

Severe hypothermia might occur with simultaneous use of this medicinal product and chlorpromazine.

The administration of Dipyrone in addition to methotrexate might increase the hepatotoxicity of methotrexate, in particular in elderly patients. This combination should therefore be avoided.

Dipyrone can reduce the effect of acetylsalicylic acid on the thrombocyte aggregation when used at the same time. Therefore, Dipyrone should be used with caution in patients who are taking acetylsalicylic acid in low doses for cardiac protection.

It is known for the substance class of pyrazolones that interactions with oral anticoagulants, captopril, lithium and triamterene and changes of the efficacy of antihypertensive agents and diuretics might occur. It is not known to what extent Dipyrone leads to these interactions.

Effect on examination methods

With Dipyrone treatment, there were reports of impairment of laboratory diagnostic investigations, which are based on the Trinder reaction or Trinder-like reactions (e.g. determination of creatinine, triglyceride, HDL cholesterol or uric acid serum levels) in patients.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is only a limited amount of data available on the use of Dipyrone in pregnant women.

Based on the published data on pregnant women who were exposed to Dipyrone during the first trimester (n = 568), no indications for teratogenic or embryotoxic effects were found. In individual cases, single doses of Dipyrone during the first and second trimester might be justified if there are no other treatment options. However, the use of Dipyrone during the first and second trimester is generally not recommended. Use during the third trimester is associated with fetotoxic effects (impairment of the kidney function and constriction of the arterial duct). The use of Dipyrone is therefore contraindicated in the third trimester of pregnancy (see section 4.3). In case of accidental use of Dipyrone in the third trimester, amniotic fluid and the arterial duct should be examined by means of ultrasound and echocardiography. Although Dipyrone is only a weak prostaglandin synthesis inhibitor, the possibility of perinatal complications due to reduction of the child's and maternal thrombocyte aggregability cannot be ruled out. Dipyrone passes the placental barrier. Animal studies showed reproduction toxicity for Dipyrone, however, no teratogenic effects were found (see section 5.3).

Lactation

Considerable amounts of degradation products of Dipyrone are excreted into breast milk and risk for a breastfed child cannot be ruled out. Particularly repeated use of Dipyrone should therefore be avoided

during breastfeeding. In case of single use of Dipyrone, it is recommended to mothers that they collect their breast milk for 48 hours after use and discard it.

4.7 Effects on the ability to drive and use machines

No influence on concentration and responsiveness is known in the recommended dose range. At least for higher dosages, possible influence should be considered as a precautionary measure, and operating machines, driving and performing other hazardous activities should be avoided. This applies in particular to interaction with alcohol.

4.8 Undesirable effects

The indication of frequency of undesirable effects is based on the following categories:

Very common (≥1/10)

Common (≥ 1/100, < 1/10)

Uncommon (≥ 1/1,000, < 1/100)

Rare (≥ 1/10,000, < 1/1,000)

Very rare (< 1/10,000)

Not known (the frequency cannot be estimated based on available data)

Diseases of the blood and the lymphatic system

Rare: Leukopenia.

Very rare: Agranulocytosis (including cases with fatal outcome), thrombocytopenia.

Not known: Aplastic anemia, pancytopenia (including cases with fatal outcome).

These reactions can also occur if Dipyrone was previously given without any complications.

This reaction does not depend on the dose and might occur at any time of treatment. It manifests itself in high fever, chills, sore throat, difficulties when swallowing and inflammation in the region of the mouth, nose, throat and genital or anal region. However, these signs can be minimal in patients receiving antibiotics. Lymph node or splenic swelling is mild or not present at all. The blood sedimentation is significantly accelerated, the granulocytes are significantly reduced or are not present at all. Generally, but not always, normal values are found for hemoglobin, erythrocytes and thrombocytes (see section 4.4).

Immediate discontinuation is essential for healing. We therefore strongly recommend discontinuing this medicinal product immediately and not deferring until the results of the laboratory tests are available, if there is an unexpected deterioration of the general condition, fever does not cease or occurs newly or painful mucosal swellings occur (in particular in the region of the mouth, nose and throat occur).

Typical signs of thrombocytopenia include increased tendency to bleeding and petechiae on the skin and the mucous membranes.

If pancytopenia occurs, treatment must be stopped immediately, and the full blood count must be monitored until it has normalized (see section 4.4).

Immune system disorders

Rare: Anaphylactoid or anaphylactic reactions*.

Very rare: Analgesic induced asthma syndrome.

Intolerability reactions manifest themselves typically in the form of asthma attacks in patients with analgesic induced asthma syndrome.

Not known: Anaphylactic shock*.

* These reactions might in particular occur after parenteral application, they might be serious and life-threatening, and in some cases even have a fatal outcome. They might also occur if Dipyrone was previously administered without any complications.

Such reactions might develop directly after administration, or hours later. However, they occur predominantly during the first hour after administration. Milder reactions manifest themselves typically in the form of skin and mucous membrane reactions (such as itching, burning sensation, reddening, urticaria, swellings), dyspnea and (in rare cases) gastrointestinal symptoms. Such mild reactions might develop into more severe forms with generalized urticaria, severe angioedema (also in the laryngeal region), severe bronchospasm, cardiac arrhythmias, hypotension (sometimes with preceding hypertension) and circulatory shock.

This medicinal product must therefore be discontinued immediately in the event of skin reactions.

Cardiac diseases:

Not known: Kounis syndrome.

Vascular diseases:

Uncommon: Hypotensive reactions during or after application, which are probably of pharmacological origin and not accompanied by other signs of an anaphylactoid or anaphylactic reaction. Such a reaction might lead to a severe hypotension.

Dose-dependent critical hypotension may also occur in the event of hyperpyrexia, without further signs of hypersensitivity.

Gastrointestinal disorders

Not known: Cases of gastrointestinal bleeding were reported.

Hepatobiliary disorders

Not known: Drug-induced liver damage, including acute hepatitis, jaundice, increased liver enzymes (see section 4.4).

Skin and subcutaneous skin disorders

Uncommon: Fixed drug eruption.

Rare: Rash (e.g. maculopapular exanthema).

Very rare: Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) (discontinue treatment).

Not known: Drug reaction with eosinophilia and systemic symptoms (DRESS).

In connection with Dipyrone treatment, severe cutaneous side effects, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS) were reported (see section 4.4).

Renal and urinary disorders

Very rare: Acute deterioration of renal function, which may progress in very rare cases to proteinuria, oliguria or anuria, or acute renal failure can develop, acute interstitial nephritis.

General disorders and administration site conditions

Red discoloring of the urine was reported, which may be attributable to the harmless Dipyrone metabolite rubazonic acid present at low concentration.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il

4.9 Overdose

Symptoms of an overdose:

In cases of acute overdose, symptoms observed include nausea, vomiting, abdominal pain, impaired kidney function/acute renal failure (e.g., presenting as interstitial nephritis), and - less frequently - central nervous system symptoms (dizziness, somnolence, coma, seizures), as well as drops in blood pressure leading to shock and tachycardia.

Discharge of rubazonic acid might cause red discoloration of the urine after very high doses.

Treatment measures in the event of overdose

No specific antidote is known for Dipyrone. If Dipyrone has only been administered a short time ago, an attempt might be made to limit the resorption into the body by means of measures of detoxification (e.g. gastric lavage) or resorption-reducing measures (e.g. active carbon). The main metabolite (4-N methylamino-antipyrine) can be eliminated by means of hemodialysis, hemofiltration, hemoperfusion or plasma filtration.

Treatment of intoxication might, like prevention of severe complications, require general and specific intensive medical monitoring and care.

Immediate measures in the event of severe hypersensitivity reactions (shock)

Stop the administration when the first signs (such as cutaneous reactions, urticaria and flush, restlessness, headaches, sweating, nausea) occur. In addition to common emergency measures such as Trendelenburg position, keeping respiratory tract free, application of oxygen, the administration of sympathomimetics, volume expanders or glucocorticoids may be necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Analgesics, other analgesics and antipyretics, pyrazolones

ATC code: N02BB02

Dipyrone is a pyrazolone derivative and it has analgesic, antipyretic and spasmolytic properties. The mechanism of action is not fully understood. Some research findings suggest that Dipyrone and the main metabolite (4-N methylamino-antipyrine) probably have both a central and a peripheral mechanism of action.

5.2 Pharmacokinetic properties

Dipyrone is completely hydrolyzed to the pharmacologically effective 4-N methylamino-antipyrine (MAA) after oral application. The bioavailability of MAA is at approximately 90% and is slightly higher after oral administration than after parenteral administration. Simultaneous intake of meals does not have any relevant impact on the kinetics of Dipyrone.

The main metabolite of Dipyrone, MAA, is further metabolized in the liver by means of oxidation and hypomethylation, followed by acetylation.

The clinical efficacy is mainly based on MAA, to a certain extent also to the metabolite 4-amino-antipyrine (AA). The area-under the curve (AUC) values for AA represent approximately 25% of the AUC values for MAA.

The metabolites 4-N acetylamino-antipyrine (AAA) and 4-N formyl amino-antipyrine (FAA) are apparently pharmacologically inactive.

Please note that all metabolites have non-linear pharmacokinetics. A clinical significance of this phenomenon is not known. The accumulation of the metabolites is of low significance for short-term treatment.

Dipyrone passes the placenta. The metabolites of Dipyrone are excreted into breast milk.

The plasma protein binding is 58% for MAA, 48% for AA, 18% for FAA and 14% for AAA.

After administration of an oral single dose, 85% of the metabolites excreted in urine could be identified. Thereof, 3 ± 1 % were MAA, 6 ± 3 % AA, 26 ± 8 % AAA and 23 ± 4 % FAA. The renal clearance after an oral single dose of 1 g Dipyrone was 5 ± 2 for MAA, 38 ± 13 for AA, 61 ± 8 for AAA and 49 ± 5 ml/min for FAA. The corresponding-plasma half-lives were 2.7 ± 0.5 hours for MAA, 3.7 ± 1.3 hours for AA, 9.5 ± 1.5 hours for AAA and 11.2 ± 1.5 hours for FAA.

Elderly patients and patients with liver dysfunction

During treatment of elderly patients, the AUC value increased by a factor two to three. After a single oral dose, patients with liver cirrhosis experienced an approximately threefold increase in the half-life of MAA and FAA, whereas the half-lives of AA and AAA did not increase to the same extent. High doses should be avoided in these patients.

Children and adolescents

Children show a more rapid elimination of the metabolites than adults.

Renal dysfunctions

The available data from patients with impaired kidney function show reduced elimination velocity for some metabolites (AAA and FAA). Therefore, high doses should be avoided in these patients.

5.3 Preclinical safety data

Investigations on sub-chronic and chronic toxicity in several animal species are available. Rats received 100 bis 900 mg Dipyrone per kg body weight orally for six months. Already after 13 weeks increase in reticulocytes and the Heinz bodies was observed in the highest dose (900 mg per kg body weight).

Dogs received Dipyrone in doses of 30 to 600 mg per kg body weight for six months. Depending on the dose, hemolytic anemia and functional changes in kidney and liver were observed from 300 mg per kg body weight.

Contradictory results are available from *in-vitro* and *in-vivo* investigations using the same test systems for Dipyrone.

Long-term examinations in rats revealed no indication of tumor-producing potential. Increased liver cell adenomas were observed in two of three long-term investigations in mice with high doses.

Embryotoxicity studies in rats and rabbits did not reveal any indication of teratogenic effects.

Embryolethal effects were observed in rabbits at a daily dose of 100 mg per kg body weight, which was not yet maternally toxic. Embryo-lethal effects occurred in rats with doses in the maternal toxicity range. Daily doses of above 100 mg per kg body weight led to prolongation of gestation period and impairment of the birth procedure with increased lethality of females and kittens in rats.

Fertility tests showed a slightly reduced pregnancy rate in the parent generation with a dose of above 250 mg per kg body weight per day. The fertility of the F1 generation was not affected.The metabolites of Dipyrone are secreted into breast milk. No experience is available about their effect on the infant.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose, Alcohol 95%, Disodium phosphate heptahydrate, Monosodium phosphate, Caramel solution, Methyl paraben, Saccharine sodium ,Polysorbate 20 (Tween 20), Propyl paraben, Orange oil, Butylated hydroxytoluene, Purified water.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the medical product is indicated on the packaging materials.

Shelf life after first opening: 1 month.

6.4 Special precautions for storage

Store in a dark place, below 25°C.

6.5 Nature and contents of container

Each package contains glass bottle (type III) with child-resistant cap liner (PP/LDPE) and a syringe, for dosage accuracy.

Approved package size: 50 ml

7. REGISTRATION HOLDER AND MANUFACTURER

Vitamed Pharmaceutical Industries Ltd.,

6 Hatahana St., P.O.B. 114, Binyamina, 3055002, Israel.

8. MARKETING AUTHORISATION NUMBER:

115-41-28046-00

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