Thromboreductin®

Composition
Each capsule contains:
Anagrelide Hydrochloride 0.57 mg equivalent to anagrelide 0.5 mg

MODE OF ACTION
Pharmacodynamic properties
In humans Anagrelide causes a dose dependent decrease in platelet count, the mechanism of action is unknown and species specific. There are no data a platelet count reducing effect in any experimental animal model, it is therefore hypothesized that Anagrelide acts via a metabolite that is generated in man. Anagrelide exerts its action via reducing the size and ploidy of megakaryocytes in the post mitotic phase of maturation. Anagrelide does not cause significant changes in white blood cells and coagulation parameters, minor changes in red blood cells were observed. When administered high, non-therapeutic doses Anagrelide inhibits the c-AMP phosphodiesterase and ADP and collagen induced thrombocyte aggregation.

Pharmacokinetic Properties
The bioavailability of anagrelide after oral administration is 70% according to data from a mass balanced study. In healthy volunteers the time to maximal plasma level (T_max) was about 1 to 2 hours, the elimination half-life is short (1 to 2 hours). Anagrelide has a high volume of distribution (120 l/kg), the distribution in different compartment is unknown, as is plasma protein binding. Anagrelide is intensively metabolised, at least 4 metabolites emerge. After administration of C14 labeled Anagrelide 75% of radioactivity are excreted within 6 days via urine, 10% via feces. The clinical experience in fasted or non-fasted patients shows that there is no effect of food on the efficacy of Anagrelide. Accumulation of Anagrelide should not occur upon long-term administration because of the short half-life. This assumption is supported by clinical experience upon stopping treatment platelet counts recover to pre-treatment levels within 4 to 8 days. No data are available for elderly patients and patients with renal or liver insufficiency. When using Anagrelide in these patients careful monitoring especially when beginning therapy should be performed (see also warnings and precautions for use).

Preclinical Safety Data
Experimental studies in different species including mice, rats, dogs and monkeys were performed for evaluation of acute and chronic toxicity. However, since the platelet reducing effect of Anagrelide cannot be reproduced in experimental animals because of the lack or insufficient metabolism into the active substance the results of these studies are of limited value for interpretation of the safety of Anagrelide. Anagrelide has been used in man for over 15 years, there is no single report described on a potential cancerogenicity, in particular no case of leukaemogenicity. A teratogenic effect has not been excluded so far. Acute Toxicity: Non-lethal doses of 2500 mg/kg, 1500 and 200 mg/kg were administered to mice, rats and monkeys. Chronic Toxicity: Long-term exposure data with different species (rat, dog and monkey) for up to 1 year were generated. There is no cancerogenicity study available. Mutagenic and cancerogenic potential: Anagrelide did not show a mutagenic potential in three in vitro and in vivo experiments. The meaning of these results is unclear, because other metabolites might emerge compared to these standard tests with metabolic activation. There is no long-term cancerogenicity study. Reproductive Toxicity: Studies for teratogenic and non-teratogenic
potential were performed in rats. Segment I and segment III studies were performed in rats, segment II studies in rats and rabbits. There was no evidence for teratogenicity. In segment I a dose dependent increase in early resorption, a prolonged period of gestation, a decrease in litter size and reduced survival index was observed. In segment III an increase in mortality and a reduced survival index in the first week of lactation was observed. Since Anagrelide exerts a species-specific effect in man, data on the reproductive toxicity in rats are of limited value. Nevertheless Anagrelide is contraindicated in pregnancy.

INDICATIONS
Thromboreductin is indicated for treatment of essential thrombocythaemia. The decision for treatment has to be taken individually for each patient depending on the number of platelets, on age, on the clinical symtomatology and anamnesis, on the speed of platelet count increase after diagnosis, on cononitant disease and risk factors for thromboembolic events, and on pre-treatment, e.g. Hydroxyurea or interferon alpha.

CONTRAINDICATIONS
Patients with known anaphylactoid reactions to the active ingredients or to adjuvant ingredients should not use Thromboreductin. Lactose intolerance has to be considered in affected patients. In clinical studies patients with cardiovascular disease grade 4, ot grade 3 with a negative benefits / risk ratio (as outlined in the exclusion criteria of the South West Oncology Group, 1992), patients with a severe renal disease (creatinin clearance < 30 ml/min) or a severe liver diseases (AST or ALT > 5 times normal) were excluded.

Pregnancy and Lactation
Anagrelide is contraindicated in in pregnant or breast feeding women. Proper contraception should be used during therapy. It is unknown whether Anagrelide is excreted in human milk.

UNDESIRABLE EFFECTS
The following adverse events occurred during therapy with Anagrelide : headache, palpitations, diarrhoea, weakness, oedema, nausea, abdominal pain, dizziness, pain, dyspnoea, flatulence, vomiting, fever, rash, chest pain, anorexia, tachycardia, pharyngitis, malaise, cough, paresthesia, back pain, pruritus, dyspepsia, flu and flu like symptom and dehydration. Most adverse events occurred during treatment initiation, were of minor intensity and diminished during ongoing therapy. Adverse events tended to decresase in number and intensity with time. In addition adverse events occurred which involved the following organs : cardiovascular system, gastro intestinal tract, haematopoietic and lymphatic system, liver, musculoskeletal system, nervous system, respiratory system, skin and skin appendages, sensory system, and urogenital tract. In case of headache (this occurs mainly upon treatment initiation) a pain medication like acetaminophen should be prescribed, in case of diarrhoea lactase (e.g. LalukÔ) should be prescribed. Lactose intolerance should be considered (see contra-indication). The following severe adverse events were observed during therapy with Anagrelide : heart failure, myocardial infarction, cardiomyopathy, heart block, atrial fibrillation, cerebrovascular events, pericarditis, pulmonary infiltrates, pulmonary fibrosis, pulmonary hypertension, pancreatitis, gastrointestinal ulcer, seizures.

WARNING AND PRECAUTIONS
Anagrelide should be used only with caution and after a careful benefit / risk evaluation in patients with cardiovascular, renal or liver diseases. When high single doses (5 mg) are
administered hypotension and dizziness may occur because of vasodilatation. Single doses of 2 mg may lead to a small transitory decrease in blood pressure. Haematological parameters (in particular haematocrit and leucocyte count), renal and liver parameters should be controlled in regular intervals during the use of Anagrelide.

**Overdose**

There are no data on overdosing of Anagrelide. According to its pharmacological mechanism of action a decrease in platelets has to be anticipated which may result in haemorrhage. Further adverse events may affect the cardiovascular system. Peripheral vasodilation may cause hypotension and tachycardia. Adverse events affecting the central nervous system, like headache and dizziness have to be expected. A careful monitoring of the overdosed patient with control of platelet count is recommended.

**DRUG INTERACTIONS**

The following drugs were used concomitantly with Anagrelide: acetylsalicylic acid, acetaminophen, furosemide, iron, ranitidine, hydroxyurea, allopurinol and digoxin. No significant interactions were reported in clinical use, however, there are no controlled interaction studies. In experimental studies on rabbits Anagrelide causes an increase in efficacy of heparin, therefore, this effect should be monitored during treatment.

**POSOLOGY AND METHOD OF ADMINISTRATION:**

Only doctors with experience in treatment of patients with essential thrombocythaemia should initiate treatment with Anagrelide. Thromboreductin has to be dosed individually for each patient. Treatment should be started with 0.5 mg/day for one week and the dose should be increased weekly by 0.5 mg/day until the desired therapeutic effect is achieved. Normally a therapeutic response is seen within 2 weeks in a dose range of 1 to 3 mg/day. The total daily dose should be administered BID (every 12 hours) or TID (every 8 hours). The total daily dose should not exceed 5 mg. The therapeutic response should be controlled regularly. Upon treatment platelet initiation counts should be measured weekly until the optimal response is reached (normalization of platelet count or a reduction to < 600,000 ml, or a decrease by 50% of baseline), afterwards platelet counts should be controlled in regular intervals according to the physician discretion. Changing a previous therapy (e.g. Hydroxyurea or Interferon alpha) to Anagrelide or to a combination therapy with Anagrelide should be done in an overlapping manner. Anagrelide is indicated for continuous use. Upon stopping treatment a relapse of platelet counts to pre-treatment levels occur within several days. In case of therapeutic resistance to Anagrelide other therapies should be considered. During therapy platelet counts should be measured regularly, every two days during the first week of treatment and at least weekly thereafter until the maintenance dosage is reached. Caution is indicated in patients with cardiovascular disease (see warnings and contraindications). Limited data are available for patients with renal and liver disease—therefore, Anagrelide should be used in these patients only under careful risk / benefits analysis. Use in elderly a limited number of elderly patients have been treated with Anagrelide. Caution is advised when treating elderly patients with cardiovascular diseases. Use in children: a limited number of a children < 16 years have been treated with Anagrelide. There seem to be no major dosing difference compared to treatment of adults.

**STORAGE**

Store below 25°C
SHELF LIFE
36 Months

PACKAGING
Box, Bottle @ 100 capsules  Reg. No. DKI0407000101A1
Box, Bottle @ 42 capsules  Reg. No. DKI0407000101A1

ON MEDICAL PRESCRIPTION ONLY
HARUS DENGAN RESEP DOKTER

Manufactured by:
Haupt Pharma GmbH
Pfaffenrieder Strajle 5,
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For:
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