Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Vesanoid 10 mg soft capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:
1 soft capsule contains 10 mg of tretinoin (all-*trans* retinoic acid, ATRA)
Excipients with known effect:
1 soft capsule contains 107.92 mg of soya-bean oil.
1 soft capsule contains 1.93 - 2.94 mg sorbitol.
For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Capsule, soft
Oval, bi-coloured orange-yellow/reddish-brown capsules.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Vesanoid (tretinoin) is indicated in combination with arsenic trioxide or chemotherapy for the treatment of patients with acute promyelocytic leukaemia (APL) which is newly diagnosed, relapsed or refractory to chemotherapy (see sections 4.2 and 5.1).
Treatment regimens
Combination of tretinoin with chemotherapy or arsenic trioxide is known to be effective and to induce very high rates of haematologic remission in patients with genetically confirmed APL, i.e. patients whose blasts harbour the t(15;17) by karyotyping or FISH or the PML-RARa fusion as detected by PCR. Thus, genetic confirmation of diagnosis is mandatory.
Combination treatment with arsenic trioxide has been shown an effective treatment option in patients with newly diagnosed low-to-intermediate risk APL. However, because APL is characterised by high risk of early haemorrhagic death, current recommendations dictate that early treatment with tretinoin is started as soon as possible upon morphologic suspicion only.
For the selection of treatment strategy the relapse risk - indicated by pre-therapeutic white blood cell count (WBC) and platelet count (Sanz score) with high-risk (WBC >$10x10^9$/L), intermediate risk (WBC ≤ $10x10^9$/L, platelet count ≤ $40x10^9$/L), and low risk (WBC ≤ $10x10^9$/L, platelet count > $40x10^9$/L) - should be taken into consideration.

4.2 Posology and method of administration

Posology
For all therapy phases a total daily dose of 45 mg/m^2 body surface divided in two equal doses is recommended for oral administration to adult and elderly APL patients. This is approximately 8 capsules per patient per day (one capsule contains 10 mg tretinoin).
Paediatric population
There is limited safety and efficacy information on the use of tretinoin in children. For children the same treatment regimen as for adults is applicable.
The optimal paediatric dose of tretinoin has not yet been established. In an attempt to reduce tretinoin related toxicity, the daily dose administered to children can be reduced to 25 mg/m^2. Dose reduction should be particularly considered for children with toxicity symptoms, such as intractable headache.
High risk patients
A treatment option for patients at high risk of disease relapse according to Sanz score (see section 4.1) is the triple combination of tretinoin, arsenic trioxide and chemotherapy (anthracyclines) for induction, followed by consolidation with tretinoin and arsenic trioxide.
Patients with hyperleukocytosis
Patients with hyperleukocytosis (see section 4.4) can receive additional chemotherapy at the very onset of induction treatment.
Patients with hepatic and/or renal impairment
Due to limited information on patients with hepatic and/or renal insufficiency, the dose will be decreased to 25 mg/m^2 as a precautionary measure.

Dose delay, modification and re-initiation

In cases of severe differentiation syndrome (DS, see section 4.4.) temporary interruption of tretinoin therapy should be considered. Treatment with tretinoin may need to be withheld during the initial acute symptomatic period, but may be resumed when symptoms resolve.

If intracranial hypertension/pseudotumour cerebri (see section 4.4.) occur, a reduction of tretinoin dose is recommended.

Method of administration

The capsules should be swallowed whole with water. They should not be chewed. It is recommended to take the capsules with a meal or shortly thereafter.

Induction therapy should be continued until complete remission has been achieved or up to a maximum of 90 days.

After completion of induction, consolidation therapy should be initiated with a tretinoin/arsenic trioxide combination or with a tretinoin/anthracycline-based chemotherapy regimen. The recommended tretinoin dose during consolidation is the same as for induction therapy, i.e. 45 mg/m^2 body surface divided in two equal doses, administered orally. Several cycles of consolidation therapy with tretinoin should be given. Current guidelines recommend that tretinoin-free intervals are included after remission and during consolidation cycles.

If maintenance therapy is given, tretinoin should be used at the same dose as for induction/consolidation therapy. The treatment regimen for maintenance therapy should include tretinoin-free intervals ("pulsed therapy"), as for consolidation therapy.

As clinical practice may vary across the EU or within national centres, national/local practice guidelines/protocols should be considered.

4.3 Contraindications

Hypersensitivity to tretinoin, retinoids, soya, peanut or to any of the excipients listed in section 6.1.

Tretinoin is teratogenic. It is contraindicated during breast-feeding (see section 4.6).

Combination with vitamin A, tetracyclines, retinoids (see section 4.5).

4.4 Special warnings and precautions for use

Tretinoin should be administered to patients with acute promyelocytic leukaemia only under the strict supervision of a physician who is experienced in the treatment of haematological / oncological diseases.

Supportive care appropriate for patients with acute promyelocytic leukaemia, for example prophylaxis for bleeding and prompt therapy for infection, should be maintained during therapy with tretinoin. The patient's haematologic profile, coagulation profile, liver function test results, and triglyceride and cholesterol levels should be monitored frequently.

Supportive measures to counteract APL-associated coagulopathy include administration of platelets transfusion to maintain a platelet count > 30-50 x10^9/L and fresh-frozen plasma or fibrinogen to maintain a fibrinogen level > 100-150 mg/dL. These values should be monitored daily and supportive care should continue during the entire induction phase until disappearance of clinical and laboratory signs of coagulopathy.

Differentiation syndrome/Retinoic Acid Syndrome

During clinical trials hyperleukocytosis has been frequently observed, sometimes associated with the "Retinoic Acid Syndrome" (RAS). RAS has been reported in many acute promyelocytic leukaemia patients treated with tretinoin (about 26% in some clinical trials) or in association with arsenic trioxide, and may be fatal. RAS is now better defined as differentiation syndrome (DS).

DS is characterised by fever, dyspnoea, acute respiratory distress, pulmonary infiltrates, hypotension, pleural and pericardial effusions, peripheral oedema, weight gain; and may progress to pulmonary, hepatic, renal and multi-organ failure. Full-blown DS is a life-threatening condition. Early recognition and treatment of DS is therefore of paramount importance. Retinoic acid syndrome is frequently associated with hyperleukocytosis (see 'Hyperleukocytosis').

An increased body mass index (BMI) has been identified as a predictor factor for DS. Therefore, patients with increased BMI should be closely monitored during therapy especially in terms of respiratory functions, diuresis and creatinine levels.

Treatment with dexamethasone (10 mg intravenously every 12 hours for a minimum of 3 days or until resolution of the symptoms) must be initiated immediately for patients who present early clinical signs of the syndrome.

In cases of severe DS, temporary interruption of tretinoin therapy should be considered.

Hyperleukocytosis

Patients experiencing hyperleukocytosis should be treated with full-dose anthracycline-based chemotherapy. Immediate treatment of patients with a white blood cell (WBC) count of ≥ 5 x 10^9/L at diagnosis or at any time during therapy is recommended.

The use of hydroxyurea should be considered for treatment of leukocytosis in patients treated with combination therapy of tretinoin with arsenic trioxide, to keep WBC < 10,000/microL

Pseudotumour cerebri

Tretinoin may cause intracranial hypertension/pseudotumour cerebri. Pseudotumour cerebri is a benign intracranial hypertension with cerebral oedema and absence of a tumour, clinically characterised by headache, papilloedema, diplopia, and possibly an altered state of consciousness.
The concomitant use of other agents known to cause intracranial hypertension /pseudotumour cerebri might increase the risk of this condition (see section 4.5).
If intracranial hypertension/pseudotumour cerebri occur, a reduction of tretinoin dose is recommended in addition to administration of diuretics (acetazolamide), corticosteroids and/or analgesics.
Paediatric population
Pseudotumour cerebri (see section 4.8) has a higher incidence in paediatric patients than in adults. Clinical trial data show a decreased incidence of pseudotumour cerebri with the use of a lower tretinoin dose, without compromising the outcome results. Therefore, a dose reduction to 25 mg/m^2 should be considered for children with toxicity symptoms, such as intractable headache (see section 4.2).
QTc prolongation
QTc prolongations have been observed in connection with combination therapy of tretinoin and arsenic trioxide. This might lead to life-threatening torsade de pointes arrhythmias.
ECG monitoring prior to, and during the course of, therapy is recommended for management of QTc prolongation, especially for patients with existing risk factors.
Hepatotoxicity
Hepatotoxicity is increased with combination therapy of tretinoin and arsenic trioxide. Liver toxicity has occurred predominantly during the first phase of therapy (induction therapy) and is mainly characterized by an increase in transaminases. The hepatic damage observed is reversible with the suspension of arsenic trioxide and/or tretinoin.
Psychiatric disorders
Depression, depression aggravated, anxiety, and mood alterations have been reported in patients treated with systemic retinoids, including tretinoin. Particular care should be taken in patients with a history of depression. Patients should be monitored for signs of depression and referred for appropriate treatment if necessary. Awareness by family or friends may be useful to detect mental health deterioration.
Others
Cases of Sweet's syndrome or acute febrile neutrophilic dermatitis responded dramatically to corticosteroid treatment.
There is a risk of thrombosis (both venous and arterial) which may involve any organ system, during the first month of treatment (see section 4.8). Therefore, caution should be exercised when treating patients with the combination of Vesanoid and antifibrinolytic agents, such as tranexamic acid, aminocaproic acid or aprotinin (see section 4.5).
Because hypercalcaemia may occur during therapy, serum calcium levels should be monitored.
Counselling for women of childbearing potential (see section 4.6)
Tretinoin is a retinoid and teratogenic effects have been seen in humans exposed to retinoid drugs. Consequently, therapy with tretinoin should only be started in a female patient of childbearing age if she is informed of the risks concerning pregnancy during tretinoin treatment. The patient must use a reliable method of contraception and pregnancy tests must be performed before treatment and at monthly intervals during therapy.
Micro-dosed progestogen preparations ("minipill") are an inadequate method of contraception during treatment with tretinoin (see section 4.6).
This medicinal product contains 1.93 - 2.94 mg sorbitol in each soft capsule.
This medicinal product contains less than 1 mmol sodium (23 mg) per soft capsule, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interactions

Contra-indicated combinations (see also section 4.3):

- Other retinoids: risk of symptoms suggestive of hypervitaminosis A.
- Vitamin A: risk of symptoms suggestive of hypervitaminosis A for daily doses greater than 10,000 IU.
- Tetracyclines: risk of intracranial hypertension (pseudotumour cerebri).

The effect of food on the bioavailability of tretinoin has not been characterised. Since the bioavailability of retinoids, as a class, is known to increase in the presence of food, it is recommended that tretinoin be administered with a meal or shortly thereafter.

As tretinoin is metabolised by the hepatic P450 system, there is the potential for alteration of pharmacokinetics parameters in patients administered concomitant medications that are also inducers or inhibitors of this system. Medications that generally induce hepatic P450 enzymes include rifampicin, glucocorticoids, phenobarbital and pentobarbital. Medications that generally inhibit hepatic P450 enzymes include ketoconazole, cimetidine, erythromycin, verapamil, diltiazem and ciclosporin. Increased toxicity of tretinoin (e.g. pseudotumour cerebri, hypercalcaemia) was reported when azole antifungals (e.g. fluconazole,

voriconazole, posaconazole) were administered. This appears to be the result of a pharmacokinetic interaction mainly involving CYP3A4. Combination with other strong CYP3A4 inhibitors (protease inhibitors or macrolides, e.g. clarithromycin), may also trigger tretinoin toxicity. A dose reduction of tretinoin should be considered if necessary.

Cases of fatal thrombotic complications have been reported rarely in patients concomitantly treated with tretinoin and antifibrinolytic agents such as tranexamic acid, aminocaproic acid and aprotinin (see section 4.4). Therefore, caution should be exercised when administering tretinoin concomitantly with these agents.

There are no data on a possible pharmacokinetic interaction between tretinoin and daunorubicin, idarubicin or cytarabine.

4.6 Fertility, pregnancy and lactation

All the measures listed below should be considered in relationship to the severity of the disease and the urgency of the treatment.

Fertility

There are no data available in humans.

Women of childbearing potential / Contraception in females

Therapy with tretinoin should only be started in a female patient of childbearing age if each of the following conditions is met:

- The patient is informed by the physician of the risks concerning pregnancy during, and for one month after, treatment with tretinoin.
- The patient is willing to comply with the mandatory contraception measures. It is absolutely essential that every woman of childbearing potential who is to undergo treatment with tretinoin uses a reliable contraception method without interruption during, and for one month after discontinuation of, treatment with tretinoin (see section 4.4).
- Pregnancy tests must be performed at monthly intervals during therapy.

Pregnancy

Tretinoin is teratogenic (see sections 4.3 and 5.3). Tretinoin is a retinoid and teratogenic effects have been seen in humans exposed to retinoid drugs.

In humans there is a limited amount of data from the use of tretinoin in pregnant women but there is a high risk of severe malformation of the foetus, particularly when tretinoin is given during the first trimester.

Vesanoid must not be used during pregnancy, especially during the first trimester, or in women of childbearing potential not using contraception, unless the clinical condition of the woman (severity of the patient's condition, urgency of the treatment) requires treatment with tretinoin.

If Vesanoid is administered in early pregnancy the patient must be warned of the teratogenic risk of Vesanoid and of the risk of severe malformation of the foetus

Breast-feeding

Breast-feeding must be discontinued if therapy with tretinoin is initiated (see section 4.3).

4.7 Effects on ability to drive and use machines

Vesanoid has minor or moderate influence on the ability to drive and use machines, particularly if patients are experiencing dizziness or severe headache.

4.8 Undesirable effects

Summary of safety profile

In patients treated with the recommended daily doses of tretinoin the most frequent undesirable effects are consistent with the signs and symptoms of the hypervitaminosis A syndrome (as for other retinoids).

Tabulated list of adverse reactions

The adverse reactions listed in the table below have been reported in pivotal clinical studies and during the post-marketing period.

Adverse reactions are presented by MedDRA System Organ Class and frequency (very common (³ 1/10)). Adverse reactions reported during the post-marketing period are also included in the table under the frequency category "not known" (cannot be estimated from the available data).

System Organ Class	Frequency	Adverse Reaction(s)
Infections and infestations	Not known	Necrotising fasciitis
Blood and lymphatic system disorders	Not known	Thrombocytosis, leukocytosis, basophilia (with or without symptomatic hyperhistaminaemia)
Metabolism and nutrition disorders	Very common	Decreased appetite
	Not known	Hypercalcaemia
Psychiatric disorders	Very common	Confusional state, anxiety, depression, insomnia
Nervous system disorders	Very common	Headache, intracranial pressure increased, pseudotumour cerebri, dizziness, paraesthesia
	Not known	Cerebrovascular accident
Eye disorders	Very common	Visual disturbances, conjunctival disorders
Ear and labyrinth disorders	Very common	Hearing impaired
Cardiac disorders	Very common	Arrhythmia
	Not known	Myocardial infarction
Vascular disorders	Very common	Flushing
	Not known	Arterial thrombosis, venous thrombosis involving various sites (e.g. cerebrovascular accident, myocardial infarction, renal infarct), vasculitis
Respiratory, thoracic and mediastinal disorders	Very common	Respiratory failure, nasal dryness, asthma
Gastrointestinal disorders	Very common	Dry mouth, nausea, vomiting, abdominal pain, diarrhoea, constipation, pancreatitis, cheilitis
Skin and subcutaneous tissue disorders	Very common	Erythema, rash, pruritus, alopecia, hyperhidrosis
	Not known	Erythema nodosum, acute febrile neutrophilic dermatosis (Sweet's syndrome)
Musculoskeletal and connective tissue disorders	Very common	Bone pain
	Not known	Myositis
Renal and urinary disorders	Not known	Renal infarct
Reproductive system and breast disorders	Not known	Genital ulceration
General disorders and administration site conditions	Very common	Chest pain, chills, malaise
Investigations	Very common	Blood triglyceride increased, blood creatinine increased, blood cholesterol increased, transaminases increased
	Not known	Histamine level increased

The decision to interrupt or continue therapy should be based on an evaluation of the benefit of the treatment versus the severity of the side-effects.

Description of selected adverse reactions

Differentiation syndrome (formerly known as retinoic acid syndrome) may be fatal and is characterised by fever, dyspnoea, acute respiratory distress, pulmonary infiltrates, pleural and pericardial effusions, hypotension, oedema, weight gain, hepatic, renal and multi-organ failure. Retinoic acid syndrome is frequently associated with hyperleukocytosis. For prevention and treatment of retinoic acid syndrome see section 4.4.

Leukocytosis/hyperleukocytosis are frequent adverse effects associated with tretinoin therapy of APL and may be accompanied by differentiation syndrome. However, most cases of leukocytosis/hyperleukocytosis are not associated with differentiation syndrome.

In clinical trials increased frequencies of hyperleukocytosis, QTc prolongation and hepatotoxic effects have been observed with combination therapy of tretinoin with arsenic trioxide compared to combination therapy of tretinoin with chemotherapy. Liver toxicity occurred predominantly during the first phase of therapy (induction therapy) and is mainly characterised by increase in transaminases. For the characteristics, prevention and treatment of hyperleukocytosis, QTc prolongation and hepatotoxic effects see section 4.4.

Teratogenicity: See section 4.6.

Paediatric population
There is limited safety information on the use of tretinoin in children. There have been some reports of increased toxicity in children treated with tretinoin, particularly increased pseudotumour cerebri (see section 4.4).

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. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Website: www.hpra.ie.

4.9 Overdose

In case of overdose with tretinoin, reversible signs of hypervitaminosis A (headache, nausea, vomiting, mucocutaneous symptoms) can appear.
The recommended dose in acute promyelocytic leukaemia is one quarter of the maximum tolerated dose in solid tumour patients (maximum dose:195 mg/m^2/day) and below the maximum tolerated dose in children (60 mg/m^2/day).
There is no specific treatment in the case of an overdose, however it is important that the patient be treated in a special haematological unit.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Cytostatic-differentiating agent, ATC code:L01XF01.
Tretinoin is a natural metabolite of retinol and belongs to the class of retinoids, comprising natural and synthetic analogues.
Mechanism of action
According to the FAB (French-American-British) classification of haematological disease, acute promyelocytic leukaemia (APL) is classified as M3 and M3v form of acute myeloid leukaemia (AML).The mechanism of action of tretinoin in APL is not entirely known, and may be linked to specific binding of tretinoin to a nuclear retinoic acid receptor (RAR) given that the nuclear receptor alpha of retinoic acid (RARa) is altered in APL patients by fusion with a protein called PML. Pharmacological doses of tretinoin induce proteolytic degradation of the PML/RARa chimeric protein, hallmark of APL. Transcriptome analyses suggest that tretinoin may clear PML/RARa from promoters, thereby restoring the wild-type RARa function and releasing the differentiation block.
Pharmacodynamic effects
In vitro studies with tretinoin have demonstrated induction of differentiation and inhibition of cell proliferation in transformed haemopoietic cell lines, including human myeloid leukaemia cell lines.
Clinical efficacy and safety
In patients suffering from acute promyelocytic leukaemia (APL), tretinoin in combination with cytotoxic chemotherapy or with arsenic trioxide inhibits proliferation and induces the differentiation of promyelocytic blasts. With such combination treatment approach high rates of complete remission and low relapse rates can be achieved.
Tretinoin combined with cytotoxic chemotherapy
The combination of tretinoin with anthracycline chemotherapeutics has been investigated in various clinical trials with children, adults, and elderly APL patients. One of the internationally established and accepted treatment regimens is the AIDA2000 protocol. In this regimen, newly diagnosed patients were treated for induction therapy with 45 mg/m^2/day tretinoin until complete remission, for a maximum of 45 days. This was followed by 3 courses of consolidation therapy with a treatment for 15 days with an equal dose in each course. During maintenance therapy, tretinoin was administered every 3 months for 15 days for 2 years. According to their relapse risk, patients received a different regimen of chemotherapy. Using this treatment approach, a 6-year overall survival of 87.4%, and a 6-year disease-free survival of 85.6% was achieved. These data are in line with other larger clinical trials (LPA99 and LPA2005, APL2000, AMLCG2009) with complete remission rates of ≥ 90%, overall survival of 82 to 94%, and disease-free survival (DFS) of 82 to 90%.
Tretinoin combined with arsenic trioxide
The combination of tretinoin with arsenic trioxide has been investigated in the APL0406 clinical trial. In this prospective, randomised, multicentre, open-label, phase III non-inferiority trial, 276 newly diagnosed patients (adults between 18 and 71 years of age) with non-high risk APL were randomly assigned to receive tretinoin/arsenic trioxide (ATO) or tretinoin/chemotherapy. Complete remission was achieved in 100% in the tretinoin/arsenic trioxide arm and 97% in the tretinoin/chemotherapy arm, respectively. After a median follow-up of 40.6 months, the event-free survival, cumulative incidence of relapse, and overall survival at 50 months for patients in the tretinoin/arsenic trioxide versus tretinoin/chemotherapy arms were 97.3% vs. 80%, 1.9% vs. 13.9%, and 99.2% vs. 92.6%, respectively ($P<0.001$, $P=0.0013$, and $P=0.0073$, respectively). Concerning the safety profiles of treatment regimen, for patients receiving tretinoin/arsenic trioxide, adverse effects mainly consisted of frequent increase of liver enzymes, QTc prolongation, and hyperleukocytosis. In almost all

patients, this toxicity was reversible and manageable with temporary drug interruption and dose adjustments as per protocol recommendations, including the addition of hydroxyurea.

Special populations

Children

In children, the treatment combining tretinoin with chemotherapy gives comparable results as with adults. For example, compared to data from adults in the APL93 trial 576 patients with 31 newly diagnosed children (5%) were investigated and no difference between adults and children was seen for complete remission rate, 5-year relapse rate, event free survival, and overall survival, but significantly better survival was seen in children after adjustment on white blood cell counts and incidence of microgranular M3 variant of APL.

In terms of toxicity and compared to adults, a higher frequency of pseudotumour cerebri has been observed in children and adolescents. The incidence decreases with the use of lower dose of tretinoin.

There are only limited data concerning the use of tretinoin in combination with arsenic trioxide in the paediatric population.

Elderly

APL is less frequently diagnosed in the elderly (patients above 60 years). Elderly patients seem at least as responsive to therapy as younger patients, but rates of response and survival are lower in this age setting owing to a higher incidence of early deaths and deaths in remission when conventional treatment with tretinoin and chemotherapy is used. The higher rate of early deaths in this cohort is due to greater comorbidities compared to those of younger patients.

There are only limited data concerning the use of tretinoin in combination with arsenic trioxide in the elderly population.

5.2 Pharmacokinetic properties

Tretinoin is an endogenous metabolite of vitamin A and is normally present in plasma.

Absorption

After oral administration, tretinoin is absorbed by the digestive tract, and maximum plasma concentrations in healthy volunteers are attained after 3 hours.

There is a large inter-patient and intra-patient variation in plasma levels of tretinoin.

Distribution

Tretinoin is extensively bound to plasma proteins. Following peak levels, plasma concentrations decline with a mean elimination half -life of 0.7 hours. Plasma concentrations return to endogenous levels following a single 40 mg dose after 7 to 12 hours. No accumulation is seen after multiple doses and tretinoin is not retained in body tissues.

Biotransformation

During continuous administration a marked decrease in plasma concentration can occur, possibly due to cytochrome P450 enzyme induction which increases clearance and decreases bioavailability after oral doses.

Tretinoin is metabolised by CYP26A1 and CYP3A4. Compounds that inhibit CYP26A1, such as ketoconazole, could result in an increase of tretinoin exposure. Clinical evidence is still lacking on the relative involvement of this enzyme in the overall metabolism of tretinoin.

Elimination

Renal excretion of metabolites formed by oxidation and glucuronidation is a major route (60%) of elimination, while 30% is excreted in the faeces. Tretinoin (all-*trans* retinoic acid) is isomerised to 13-cis retinoic acid and oxidised to 4-oxo-metabolites. These metabolites have longer half-lives than tretinoin and may show some accumulation.

Renal and hepatic impairment

The requirement for dosage adjustment in patients with kidney or liver dysfunction has not been investigated. As a precautionary measure, the dose should be decreased to 25 mg/m^2/day (see section 4.2).

5.3 Preclinical safety data

Oral administration of tretinoin to animals indicated that the compound had very low acute toxicity in all species investigated.

In animal experimental tests it was shown that in all investigated species the acute toxicity of tretinoin administered orally is low. After a longer period of administration rats exhibit a dose- and time-dependent bone matrix dissolution, a decrease in erythrocyte count and toxic alterations in kidney and testes.

Dogs mainly exhibited disorders concerning spermatogenesis and hyperplasia of the bone marrow.

The major metabolites of tretinoin (4-oxo-tretinoin, isotretinoin and 4-oxo-isotretinoin) are less effective than tretinoin in inducing differentiation of human leukaemic cells (HL-60).

Sub-chronic and chronic toxicity studies in rats indicated that the no effect oral dose was at or below 1 mg/kg/day; in dogs, 30 mg/kg/day was associated with toxic effects including weight loss, dermatological and testicular changes.

Reproduction studies in animals have demonstrated the teratogenic activity of tretinoin.

No evidence of mutagenicity has been found.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents
Yellow beeswax
Hydrogenated soya-bean oil
Partially hydrogenated soya-bean oil
Soya-bean oil

Capsule shell
Gelatin
Glycerol (E 422)
Karion 83: Sorbitol, Mannitol, Starch (maize)
Titanium dioxide (E 171)
Iron oxide yellow (E 172)
Iron oxide red (E 172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Bottles
Do not store above 30°C.

Keep the bottle tightly closed in order to protect from moisture.

Keep the bottle in the outer carton in order to protect from light.

6.5 Nature and contents of container

Amber glass bottles of 100 capsules.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

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

Use and handling: No special requirements.

7 MARKETING AUTHORISATION HOLDER

Cheplapharm Arzneimittel GmbH
Ziegelhof 24
17489 Greifswald
Germany

8 MARKETING AUTHORISATION NUMBER

PA1868/001/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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