SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Allopurinol Sandoz tablet 100 mg, tabletten
Allopurinol Sandoz tablet 300 mg, tabletten

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

[Nationally completed name] 100 mg tablets
Each tablet contains 100 mg of allopurinol.

Excipients with known effect
Each tablet contains 35 mg of lactose (as monohydrate)

[Nationally completed name] 300 mg tablets
Each tablet contains 300 mg of allopurinol.

Excipients with known effect
Each tablet contains 106 mg of lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

[Nationally completed name] 100 mg tablets

white to off white, scored, flat cylindrical tablet debossed with ‘I’ and ‘56’ on either side of the break line on one side and plain on other side. Diameter: approx. 8 mm.

[Nationally completed name] 300 mg tablets

white to off white, scored, flat cylindrical tablet debossed with ‘I’ and ‘57’ on either side of the break line on one side and plain on other side. Diameter: approx. 11 mm.

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults

- All forms of hyperuricaemia not controllable by diet, including secondary hyperuricaemia of differing origin and clinical complications of hyperuricaemic states, particularly manifest gout, urate nephropathy and for the dissolution and prevention of uric acid stones.

- The management of recurrent mixed calcium oxalate stones in concurrent hyperuricaemia, when fluid, dietary and similar measures have failed.

Children and adolescents

- Secondary hyperuricaemia of differing origin

- Uric acid nephropathy during treatment of leukaemia

- Hereditary enzyme deficiency disorders, Lesch-Nyhan syndrome (partial or total hypoxanthin-guanin phosphoribosyl transferase deficiency) and adenine phosophoribosyl transferase deficiency.

4.2 Posology and method of administration

Posology

Adults
[Nationally completed name] should be introduced at low dose e.g. 100mg/day to reduce the risk of adverse reactions and increased only if the serum urate response is unsatisfactory. Extra caution should be exercised if renal function is poor (see *Renal impairment*).

The following dose schedules are suggested:
100 to 200 mg daily in mild conditions,
300 to 600 mg daily in moderately severe conditions,
700 to 900 mg daily in severe conditions.
If dose on a mg/kg bodyweight basis is required, 2 to 10 mg/kg bodyweight/day should be used.

Pediatric population
[Nationally completed name 100 mg tablets]
Paediatric population ≥15 kg bodyweight
[Nationally completed name 300 mg tablets]
Paediatric population ≥45 kg bodyweight

Children under 15 years: 10 to 20 mg/kg bodyweight/day up to a maximum of 400 mg daily given as 3 divided doses.
Use in children is rarely indicated, except in malignant conditions (especially leukaemia) and certain enzyme disorders such as Lesch-Nyhan syndrome.

Elderly
In the absence of specific data, the lowest dose which produces satisfactory urate reduction should be used. Particular attention should be paid to advice in *Renal impairment* and section 4.4.

Renal impairment
Since allopurinol and its metabolites are excreted by the kidney, impaired renal function may lead to retention of the medicinal product and/or its metabolites with consequent prolongation of plasma half-lives.

The following schedule may serve as guidance for dose adjustments at renal impairment:

Creatinine Clearance	**Daily Dose**
> 20 ml/min	normal dose
10 to 20 ml/min	100 to 200 mg per day
< 10 ml/min	100 mg/day or longer dose intervals

In severe renal insufficiency, it may be advisable to use less than 100 mg per day or to use single doses of 100 mg at longer intervals than one day.

If facilities are available to monitor plasma oxipurinol concentrations, the dose should be adjusted to maintain plasma oxipurinol levels below 100micromol/litre (15.2 mg/litre).

Allopurinol and its metabolites are removed by renal dialysis. If dialysis is required two to three times a week consideration should be given to an alternative dose schedule of 300-400 mg [Nationally completed name] immediately after each dialysis with none in the interim.

Hepatic impairment
Reduced doses should be used in patients with hepatic impairment. Periodic liver function tests are recommended during the early stages of therapy.

Treatment of high urate turnover conditions, e.g. neoplasia, Lesch-Nyhan syndrome
It is advisable to correct existing hyperuricaemia and/or hyperuricosuria with [Nationally completed name] before starting cytotoxic therapy. It is important to ensure adequate hydration to maintain optimum diuresis and to attempt alkalinisation of urine to increase solubility of urinary urate/uric acid. Dose of [Nationally completed name] should be at the lower end of the recommended dose schedule.

If urate nephropathy or other pathology has compromised renal function, the advice given in *Renal impairment* should be followed.

These steps may reduce the risk of xanthine and/or oxipurinol deposition complicating the clinical situation. See also sections 4.5 and 4.8.

Monitoring Advice
The dose should be adjusted by monitoring serum urate concentrations and urinary urate/uric acid levels at appropriate intervals.

Method of administration
[Nationally completed name] may be taken orally once a day after a meal. If the daily dose exceeds 300 mg and gastrointestinal intolerance is evident, a divided doses regimen may be appropriate.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Hypersensitivity syndrome, SJS and TEN
Allopurinol hypersensitivity reactions can manifest in many different ways, including maculopapular exanthema, hypersensitivity syndrome (also known as DRESS) and Stevens-Johnson Syndrome (SJS)/toxic epidermal necrolysis (TEN).
These reactions are clinical diagnoses, and their clinical presentations remain the basis for decision making. If such reactions occur at any time during treatment, allopurinol should be withdrawn immediately. Rechallenge should not be undertaken in patients with hypersensitivity syndrome and SJS/TEN. Corticosteroids may be beneficial in overcoming hypersensitivity skin reactions.

HLA-B*5801 allele
The HLA-B*5801 allele has been shown to be associated with the risk of developing allopurinol related hypersensitivity syndrome and SJS/TEN. The frequency of the HLA- B*5801 allele varies widely between ethnic populations being up to 20% in Han Chinese population, 8-15% in the Thai, about 12% in the Korean population and 1-2% in individuals of Japanese or European origin. Screening for HLA-B*5801 should be considered before starting treatment with allopurinol in patient subgroups where the prevalence of this allele is known to be high. Chronic kidney disease may increase the risk in these patients additionally. In case that no HLA-B*5801 genotyping is available for patients with Han Chinese, Thai or Korean descent the benefits should be thoroughly assessed and considered outweigh the possible higher risks before starting therapy. The use of genotyping has not been established in other patient populations. If the patient is a known carrier of HLA-B*5801 (especially in those who are from Han Chinese, Thai or Korean descent, allopurinol should not be started unless there are no other reasonable therapeutic options and benefits are thought to exceed risks. Extra vigilance for signs of hypersensitivity syndrome or SJS/TEN is required and the patient should be informed of the need to stop treatment immediately at the first appearance of symptoms.

SJS/TEN can still occur in patients who are found to be negative for HLA-B*5801 irrespective of their ethnic origin.

Chronic renal impairment
Chronic renal impairment and concomitant use of diuretics, especially thiazides, has been associated with an increased risk of allopurinol-induced SJS-/TEN syndrome and other severe hypersensitivity reactions.

Hepatic or renal impairment
Reduced doses should be used in patients with hepatic or renal impairment. (See section 4.2) Patients under treatment for hypertension or cardiac insufficiency, for example with diuretics or ACE inhibitors, may have some concomitant impairment of renal function and allopurinol should be used with care in this group.

Asymptomatic hyperuricaemia per se is generally not considered an indication for use of allopurinol. Fluid and dietary modification with management of the underlying cause may correct the condition.

Acute gouty attacks

Allopurinol treatment should not be started until an acute attack of gout has completely subsided, as further attacks may be precipitated.

In the early stages of treatment with [Nationally completed name], as with uricosuric agents, an acute attack of gouty arthritis may be precipitated. Therefore it is advisable to give prophylaxis with a suitable anti-inflammatory agent or colchicine for at least one month. The literature should be consulted for details of appropriate dose and precautions and warnings.

If acute attacks develop in patients receiving allopurinol, treatment should continue at the same dose while the acute attack is treated with a suitable anti-inflammatory agent.

Xanthine deposition
In conditions where the rate of urate formation is greatly increased (e.g. malignant disease and its treatment, Lesch-Nyhan syndrome) the absolute concentration of xanthine in urine could, in rare cases, rise sufficiently to allow deposition in the urinary tract. This risk may be minimised by adequate hydration to achieve optimal urine dilution.

Impaction of uric acid renal stones
Adequate therapy with [Nationally completed name] will lead to dissolution of large uric acid renal pelvic stones, with the remote possibility of impaction in the ureter.

Thyroid disorders
Increased TSH values (>5.5 µIU/mL) were observed in patients on long-term treatment with allopurinol (5.8%) in a long term open label extension study. Caution is required when allopurinol is used in patients with alteration of thyroid function.

[Nationally completed name] contain lactose
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Cytostatics
With administration of allopurinol and cytostatics (e.g. cyclophosphamide, doxorubicin, bleomycin, procarbazine, alkyl halogenides), blood dyscrasias occur more frequently than when these active substances are administered alone.
Blood count monitoring should therefore be performed at regular intervals.

Aluminium hydroxide
If aluminium hydroxide is taken concomitantly, allopurinol may have an attenuated effect. There should be an interval of at least 3 hours between taking both medicinal products.

6-mercaptopurine and azathioprine
Azathioprine is metabolised to 6-mercaptopurine which is inactivated by the action of xanthine oxidase. When 6-mercaptopurine or azathioprine is given concurrently with allopurinol, only one-quarter of the usual dose of 6-mercaptopurine or azathioprine should be given because inhibition of xanthine oxidase will prolong their activity.

Vidarabine (Adenine Arabinoside)
Evidence suggests that the plasma half-life of vidarabine is increased in the presence of allopurinol. When the two products are used concomitantly extra vigilance is necessary, to recognise enhanced toxic effects.

Salicylates and uricosuric agents
Oxipurinol, the major metabolite of allopurinol and itself therapeutically active, is excreted by the kidney in a similar way to urate. Hence, medicinal products with uricosuric activity such as probenecid or large doses of salicylate may accelerate the excretion of oxipurinol. This may decrease the therapeutic activity of allopurinol, but the significance needs to be assessed in each case.

Chlorpropamide
If allopurinol is given concomitantly with chlorpropamide when renal function is poor, there may be an increased risk of prolonged hypoglycaemic activity because allopurinol and chlorpropamide may compete for excretion in the renal tubule.

Coumarin anticoagulants
There have been rare reports of increased effect of warfarin and other coumarin anticoagulants when co-administered with allopurinol, therefore, all patients receiving anticoagulants must be carefully monitored.

Phenytoin
Allopurinol may inhibit hepatic oxidation of phenytoin but the clinical significance has not been demonstrated.

Theophylline
Inhibition of the metabolism of theophylline has been reported. The mechanism of the interaction may be explained by xanthine oxidase being involved in the biotransformation of theophylline in man. Theophylline levels should be monitored in patients starting or increasing allopurinol therapy.

Ampicillin/Amoxicillin
An increase in frequency of skin rash has been reported among patients receiving ampicillin or amoxicillin concurrently with allopurinol compared to patients who are not receiving both medicinal products. The cause of the reported association has not been established. However, it is recommended that in patients receiving allopurinol an alternative to ampicillin or amoxicillin is used where available.

Ciclosporin
Reports suggest that the plasma concentration of ciclosporin may be increased during concomitant treatment with allopurinol. The possibility of enhanced ciclosporin toxicity should be considered if the medicinal products are co-administered.

Didanosine
In healthy volunteers and HIV patients receiving didanosine, plasma didanosine C_{max} and AUC values were approximately doubled with concomitant allopurinol treatment (300 mg daily) without affecting terminal half-life. Co-administration of these 2 medicinal products is generally not recommended. If concomitant use is unavoidable, a dose reduction of didanosine may be required, and patients should be closely monitored.

Diuretics
There have been reports of interactions between allopurinol and furosemide which causes increased serum urate and plasma oxipurinol levels. Increased risk of hypersensitivity has been reported when allopurinol has been administered with diuretics, especially with thiazides and especially with reduced renal function.

Angiotensin converting enzyme (ACE) inhibitors
Increased risk of hypersensitivity has been reported when allopurinol has been administered with ACE inhibitors, especially with reduced renal function.

Captopril
With concomitant administration of allopurinol and captopril, the risk of skin reactions can be raised, especially in cases of chronic renal failure.

4.6 Fertility, pregnancy and lactation

Pregnancy
There is insufficient evidence of safety of allopurinol in human pregnancy. Animal reproductive toxicity studies have shown conflicting results (see section 5.3).
Use in pregnancy only where there is no safer alternative and when the disease itself carries risks for the mother or unborn child.

Breast-feeding
Allopurinol and its metabolite oxipurinol is excreted in the human breast milk. Allopurinol during breast-feeding is not recommended.
Concentrations of 1.4 mg/litre allopurinol and 53.7 mg/litre oxipurinol have been demonstrated in breast milk from woman taking allopurinol 300 mg/day. However, there are no data concerning the effects of allopurinol or its metabolites on the breast-fed baby.
A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from allopurinol therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

4.7 Effects on ability to drive and use machines

Since adverse reactions such as vertigo, somnolence and ataxia have been reported in patients receiving allopurinol, patients should exercise caution before driving, using machinery or participating in dangerous activities until they are reasonably certain that allopurinol does not adversely affect performance.

4.8 Undesirable effects

For this product there is no modern clinical documentation which can be used as support for determining the frequency of undesirable effects. Undesirable effects may vary in their incidence depending on the dose received and also when given in combination with other therapeutic agents.

The frequency categories assigned to the adverse reactions below are estimates: for most reactions, suitable data for calculating incidence are not available. Adverse reactions identified through post-

marketing surveillance were considered to be rare or very rare. The following convention has been used for the classification of frequency:

Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000)
Not known (cannot be estimated from the available data)

The incidence of adverse reactions is higher in the presence of renal and/or hepatic disorder.

Table 1 Undesirable effects		
System Organ Class	**Frequency**	**Adverse reaction**
Infections and infestations	Very rare	Furuncle
Blood and lymphatic system disorders	Very rare	Aranulocytosis[1] Aplastic anaemia[1] Thrombocytopenia[1]
Immune system disorders	Uncommon	Hypersensitivity[2]
	Very rare	Angioimmunoblastic lymphadenopathy[3], Anaphylactic reaction
Metabolism and nutrition disorders	Very rare	Diabetes mellitus Hyperlipidaemia
Psychiatric disorders	Very rare	Depression
Nervous system disorders	Very rare	Coma Paralysis Ataxia Neuropathy peripheral Paraesthesia Somnolence Headache Dysgeusia
	Not known	Aseptic meningitis
Eye disorders	Very rare	Cataract Visual impairment Maculopathy
Ear and labyrinth disorders	Very rare	Vertigo
Cardiac disorders	Very rare	Angina pectoris Bradycardia
Vascular disorders	Very rare	Hypertension

Gastrointestinal disorders	Uncommon	Vomiting[4] Nausea[4] Diarrhoea
	Very rare	Haematemesis Steatorrhoea Stomatitis Change of bowel habit
Hepatobiliary disorders	Uncommon	Liver function test abnormal[5]
	Rare	Hepatitis (including hepatic necrosis and granulomatous hepatitis)[5]
Skin and subcutaneous tissue disorders	Common	Rash
	Rare	Stevens-Johnson syndrome/toxic epidermal necrolysis[6]
	Very rare	Angioedema[7] Drug eruption Alopecia Hair colour changes
Renal and urinary disorders	Very rare	Haematuria Azotaemia
Reproductive system and breast disorders	Very rare	Infertility male Erectile dysfunction Gynaecomastia
General disorders and administration site conditions	Very rare	Oedema Malaise Asthenia Pyrexia[8]
Investigations	Common	blood thyroid stimulating hormone increased[9]

[1] Very rare reports have been received of thrombocytopenia, agranulocytosis and aplastic anaemia, particularly in individuals with impaired renal and/or hepatic function, reinforcing the need for particular care in this group of patients.

[2] A delayed multi-organ hypersensitivity disorder (known as hypersensitivity syndrome or DRESS) with fever, rashes, vasculitis, lymphadenopathy, pseudo lymphoma, arthralgia, leucopenia, eosinophilia hepato-splenomegaly, abnormal liver function tests and vanishing bile duct syndrome (destruction and disappearance of the intrahepatic bile ducts) occurring in various combinations. Other organs may also be affected (e.g. liver, lungs, kidneys, pancreas, myocardium, and colon). If such reactions do occur, it may be at any time during treatment, allopurinol should be withdrawn IMMEDIATELY and PERMANENTLY.

Rechallenge should not be undertaken in patients with hypersensitivity syndrome and SJS/TEN. Corticosteroids may be beneficial in overcoming hypersensitivity skin reactions. When generalised

hypersensitivity reactions have occurred, renal and/or hepatic disorder has usually been present particularly when the outcome has been fatal.

[3] Angioimmunoblastic lymphadenopathy has been described very rarely following biopsy of a generalized lymphadenopathy. It appears to be reversible on withdrawal of allopurinol.

[4] In early clinical studies, nausea and vomiting were reported. Further reports suggest that this reaction is not a significant problem and can be avoided by taking allopurinol after meals.

[5] Hepatic dysfunction has been reported without overt evidence of more generalised hypersensitivity.

[6] Skin reactions are the most common reactions and may occur at any time during treatment. They may be pruritic, maculopapular, sometimes scaly, sometimes purpuric and rarely exfoliative, such as Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN). Allopurinol should be withdrawn IMMEDIATELY should such reactions occur. The highest risk for SJS and TEN, or other serious hypersensitivity reactions, is within the first weeks of treatment. The best results in managing such reactions come from early diagnosis and immediate discontinuation of any suspect medicinal product. After recovery from mild reactions, allopurinol may, if desired, be re-introduced at a small dose (e.g. 50 mg/day) and gradually increased. The HLA-B*5801 allele has been shown to be associated with the risk of developing allopurinol related hypersensitivity syndrome and SJS/TEN. The use of genotyping as a screening tool to make decisions about treatment with allopurinol has not been established. If the rash reoccurs, allopurinol should be PERMANENTLY withdrawn as more severe hypersensitivity reactions may occur (see Immune system disorders). If SJS/TEN, or other serious hypersensitivity reactions cannot be ruled out, DO NOT re-introduce allopurinol due to the potential for a severe or even fatal reaction. The clinical diagnosis of SJS/TEN, or other serious hypersensitivity reactions remain the basis for decision making.

[7] Angioedema has been reported to occur with and without signs and symptoms of a more generalised hypersensitivity reaction.

[8] Fever has been reported to occur with and without signs and symptoms of a more generalised allopurinol hypersensitivity reaction (see Immune system disorders).

[9] The occurrence of increased thyroid stimulating hormone (TSH) in the relevant studies did not report any impact on free T4 levels or had TSH levels indicative of subclinical hypothyroidism.

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 the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms and Signs
Ingestion of up to 22.5 g allopurinol without adverse reaction has been reported. Symptoms and signs including nausea, vomiting, diarrhoea and dizziness have been reported in a patient who ingested 20 g allopurinol. Recovery followed general supportive measures.

Management
Massive absorption of [Nationally completed name] may lead to considerable inhibition of xanthine oxidase activity, which should have no untoward effects unless affecting concomitant medicinal product especially with 6-mercaptopurine and/or azathioprine.
Adequate hydration to maintain optimum diuresis facilitates excretion of allopurinol and its metabolites. If considered necessary haemodialysis may be used.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antigout preparations, preparations inhibiting uric acid production

ATC code: M04AA01

Allopurinol is a xanthine-oxidase inhibitor. Allopurinol and its main metabolite oxipurinol lower the level of uric acid in plasma and urine by inhibition of xanthine oxidase, the enzyme catalyzing the oxidation of hypoxanthine to xanthine and xanthine to uric acid. In addition to the inhibition of purine catabolism in some but not all hyperuricaemic patients, de novo purine biosynthesis is depressed via feedback inhibition of hypoxanthine-guanine phosphoribosyltransferase. Other metabolites of allopurinol include allopurinol-riboside and oxipurinol-7 riboside.

5.2 Pharmacokinetic properties

Absorption
Allopurinol is active when given orally and is rapidly absorbed from the upper gastrointestinal tract. Studies have detected allopurinol in the blood 30-60 minutes after dosing. Estimates of bioavailability vary from 67% to 90%. Peak plasma levels of allopurinol generally occur approximately 1.5 hours after oral administration of allopurinol, but fall rapidly and are barely detectable after 6 hours. Peak levels of oxipurinol generally occur after 3-5 hours after oral administration of allopurinol and are much more sustained.

Distribution
Allopurinol is negligibly bound by plasma proteins and therefore variations in protein binding are not thought to significantly alter clearance. The apparent volume of distribution of allopurinol is approximately 1.6 litre/kg which suggests relatively extensive uptake by tissues. Tissue concentrations of allopurinol have not been reported in humans, but it is likely that allopurinol and oxipurinol will be present in the highest concentrations in the liver and intestinal mucosa where xanthine oxidase activity is high.

Biotransformation
Approximately 20% of the ingested allopurinol is excreted in the faeces. Elimination of allopurinol is mainly by metabolic conversion to oxipurinol by xanthine oxidase and aldehyde oxidase, with less than 10% of the unchanged allopurinol excreted in the urine. Allopurinol has a plasma half-life of about 1 to 2 hours.

Oxipurinol is a less potent inhibitor of xanthine oxidase than allopurinol, but the plasma half- life of oxipurinol is far more prolonged. Estimates range from 13 to 30 hours in man. Therefore effective inhibition of xanthine oxidase is maintained over a 24 hour period with a single daily dose of allopurionol. Patients with normal renal function will gradually accumulate oxipurinol until a steady-state plasma oxipurinol concentration is reached. Such patients, taking 300 mg of allopurinol per day will generally have plasma oxipurinol concentrations of 5-10 mg/litre.

Elimination
Oxipurinol is eliminated unchanged in the urine but has a long elimination half-life because it undergoes tubular reabsorption. Reported values for the elimination half-life range from 13.6 hours to 29 hours. The large discrepancies in these values may be accounted for by variations in study design and/or creatinine clearance in the patients.

Pharmacokinetics in renal impairment

Allopurinol and oxipurinol clearance is greatly reduced in patients with poor renal function resulting in higher plasma levels in chronic therapy. Patients with renal impairment, where creatinine clearance values were between 10 and 20 ml/min, showed plasma oxipurinol concentrations of approximately 30mg/litre after prolonged treatment with 300 mg allopurinol per day. This is approximately the concentration which would be achieved by doses of 600 mg/day in those with normal renal function. A reduction in the dose of Allopurinol is therefore required in patients with renal impairment.

Pharmacokinetics in elderly

The kinetics of the medicinal product are not likely to be altered other than due to deterioration in renal function (see Pharmocokinetics in renal impairment).

5.3 Preclinical safety data

Teratogenicity

One study in mice receiving intraperitoneal doses of 50 or 100 mg/kg on days 10 or 13 of gestation resulted in foetal abnormalities, however in a similar study in rats at 120 mg/kg on day 12 of gestation no abnormalities were observed. Extensive studies of high oral doses of allopurinol in mice up to 100 mg/kg/day, rats up to 200 mg/kg/day and rabbits up to 150 mg/kg/day during days 8 to 16 of gestation produced no teratogenic effects.

An *in vitro* study using foetal mouse salivary glands in culture to detect embryotoxicity indicated that allopurinol would not be expected to cause embryotoxicity without also causing maternal toxicity.

In animal experiments, long-term application of high doses of allopurinol resulted in formation of xanthin precipitates (urolithiasis), which led to morphological changes in uriniferous organs.

There are no additional non-clinical data considered relevant to clinical safety beyond those included in other sections of this SPC.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose Monohydrate
Maize Starch
Povidone
Magnesium Stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

HDPE bottle:
Shelf life after first opening: 6 months

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

[Nationally completed name] 100 mg tablets

Blister: PVC/Alu
Pack sizes: 20, 30, 50, 60, 100 tablets
30 x 1 tablets unit-dose

Bottle: HDPE container with PP child resistant cap, or with PP non-child resistant cap with induction seal
Pack sizes: 50, 100, 105, 125, 250, 500 tablets

[Nationally completed name] 300 mg tablets

Blister: PVC/Alu
Pack sizes: 30, 60, 100 tablets
30 x 1 tablets unit dose

Bottle: HDPE container with PP child resistant cap
Pack sizes: 100, 105, 125 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

7. HOUDER VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN

Sandoz B.V.
Veluwezoom 22
1327 AH Almere
Nederland

8. NUMMER(S) VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN

RVG 117525, Allopurinol Sandoz tablet 100 mg
RVG 117526, Allopurinol Sandoz tablet 300 mg

9. DATUM VAN EERSTE VERLENING VAN DE VERGUNNING/VERLENGING VAN DE VERGUNNING

Datum van eerste verlening van de vergunning: 7 november 2016
Datum van laatste verlening: 31 mei 2021

10. DATUM VAN HERZIENING VAN DE TEKST

Laatste gedeeltelijke wijziging betreft rubriek 4.8: 23 december 2021