SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ketosteril film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One film-coated tablet contains:

(RS)-3-methyl-2-oxovaleric acid (α-ketoanalogue to DL-isoleucine), calcium-salt	67 mg
4-methyl-2-oxovaleric acid (α-ketoanalogue to leucine), calcium-salt	101 mg
2-oxo-3-phenylpropionic acid (α-ketoanalogue to phenylalanine), calcium-salt	68 mg
3-methyl-2-oxobutyric acid (α-ketoanalogue to valine), calcium salt	86 mg
(RS)-2-hydroxy-4-methylthio-butyric acid (α-hydroxyanalogue to DL-methionine), calcium-salt	59 mg
L-lysine acetate corresponding to 75 mg L-lysine	105 mg
L-threonine	53 mg
L-tryptophan	23 mg
L-histidine	38 mg
L-tyrosine	30 mg
Total nitrogen content per tablet	36 mg
Calcium content per tablet	1.25 mmol = 50 mg

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Oblong, yellow film-coated tablet

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prevention and treatment of damages due to faulty or deficient protein metabolism in chronic kidney disease in connection with a limited dietary protein intake of 40 g/day or less (adult). Usually this applies to patients whose glomerular filtration rate (GFR) is less than 25 mL/min.

4.2 Posology and method of administration

Posology
If not otherwise prescribed the dose for adults (70 kg body weight) is 4 to 8 tablets three times daily during meals. The tablets must not be chewed.

Ingestion during meals facilitates proper absorption and the metabolisation into the corresponding amino acids.

Paediatric population
There is no experience in children (see section 4.4).

Method of administration
For oral use.

Duration of administration
Ketosteril tablets are administered as long as the glomerular filtration rate (GFR) is below 25 mL/min, and concomitantly, dietary protein is restricted to 40 g/day or less (adult).

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1
Hypercalcaemia
Disturbed amino acid metabolism

4.4 Special warnings and precautions for use

The serum calcium level should be monitored regularly.
Ensure sufficient calorie intake.
In the presence of hereditary phenylketonuria, attention should be given to the fact that Ketosteril contains phenylalanine.
Monitoring of the serum phosphate levels is needed in case of concomitant administration of aluminium hydroxide (see section 4.5).

Paediatric population
No experience has been gained so far with the administration in paediatric patients.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant administration of calcium-containing drugs may cause or aggravate elevated serum calcium levels.

Drugs that form hardly soluble compounds with calcium (e.g. tetracyclines, quinolines such as ciprofloxacin and norfloxacin as well as drugs containing iron, fluoride or estramustine) should not be taken at the same time with Ketosteril to avoid disturbed absorption of the active substances. An interval of at least two hours should elapse between the ingestion of Ketosteril and these drugs.

The susceptibility to cardioactive glycosides, and hence the risk for arrhythmia will increase if Ketosteril produces elevated serum calcium levels (see section 4.8).

Uraemic symptoms improve under therapy with Ketosteril. Thus, in case of aluminium hydroxide administration, the dose of this drug has to be reduced if necessary. Serum phosphate levels should be monitored for a decrease.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of Ketosteril in pregnant women.
Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3).
Caution should be exercised when prescribing to pregnant women.

Breastfeeding
No experience has been made so far with the use during lactation.

4.7 Effects on ability to drive and use machines

Ketosteril has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Adverse effect frequencies are ranked as follows:

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)

	Very rare (<1/10000)
Metabolism and nutrition disorders	Hypercalcaemia

If hypercalcaemia occurs, the intake of vitamin D should be reduced. In case of persisting hypercalcaemia, the dose of Ketosteril as well as the intake of any other calcium sources has to be reduced. (See also section 4.5)

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. [*to be completed nationally*]

4.9 Overdose

No case of overdose has been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Amino acids, including combinations with polypeptides, ATC code: V06DD

Ketosteril tablets are administered for nutrition therapy in chronic kidney disease.
Ketosteril allows the intake of essential amino acids while minimising the amino-nitrogen intake.

Following absorption, the keto- and hydroxy-analogues are transaminated to the corresponding essential amino acids by taking nitrogen from non-essential amino acids, thereby decreasing the formation of urea by re-using the amino group. Hence, the accumulation of uraemic toxins is reduced. Keto and hydroxy acids do not induce hyperfiltration of the residual nephrons. Ketoacid containing supplements exert a positive effect on renal hyperphosphataemia and secondary hyperparathyroidism. Moreover, renal osteodystrophy may be improved. The use of Ketosteril in combination with a very low protein diet allows to reduce nitrogen intake while preventing the deleterious consequences of inadequate dietary protein intake and malnutrition.

5.2 Pharmacokinetic properties

The plasma kinetics of amino acids and their integration in the metabolic pathways are well established. It should nevertheless be noted that in uraemic patients, the cause of the changed plasma levels, which occur frequently in these patients, does not seem to be the absorption of the supplied amino acids, i. e. the absorption itself is not disturbed. The changed plasma levels seem to be due to impaired post-absorptive kinetics, which can be detected in a very early stage of the disease.

In healthy individuals, the plasma levels of ketoacids increase within 10 min after oral administration. Increases of up to the 5-fold the baseline levels are achieved. Peak levels occur within 20-60 min, and after 90 min levels stabilise in the range of the base levels. Gastrointestinal absorption is thus very rapid. The simultaneous increases in the levels of the ketoacids and the corresponding amino acids show that the ketoacids are transaminated very rapidly. Due to the physiological utilisation pathways of ketoacids in the body it is likely that exogenously supplied ketoacids are very rapidly integrated into the metabolic cycles. Ketoacids follow the same catabolic pathways as classical amino acids. No specific study on ketoacid excretion has been performed to date.

5.3 Preclinical safety data

Preclinical data reveal no special hazards for humans based on conventional studies on pharmacological safety, acute and repeated dose toxicity, reproduction toxicity, and genotoxicity.
Ketosteril does not show teratogenic properties.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Maize starch
- Crospovidone type A
- Talc
- Silica, colloidal anhydrous
- Magnesium stearate (Ph.Eur) [vegetable]
- Macrogol 6000
- Quinoline yellow E104
- Basic butylated methacrylate copolymer
- Triacetin
- Titanium dioxide E171
- Povidone K 29-32

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 25 °C.
Store in the original package and keep the blisters tightly closed to protect contents from moisture.

6.5 Nature and contents of container

Pack containing aluminium bags with 100 or 300 film-coated tablets in blisters.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

[To be completed nationally]

8. MARKETING AUTHORISATION NUMBER

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

[To be completed nationally]