SUMMARY OF PRODUCT CHARACTERISTICS

1) **PRODUCT NAME: normast®**

2) **QUALITATIVE AND QUANTITATIVE COMPOSITION**
Active Principle:
normast® 300 micronized Palmitoylethanolamide 300mg each tablet;
normast® 600 ultra-micronized Palmitoylethanolamide 600mg each tablet;
normast® 600 Microgranules ultra-micronized Palmitoylethanolamide 600mg each sachet;
Excipients: single tablets of **normast®** 300mg and 600mg contain 141,47 mg and 282,94 mg respectively of a mixture of excipients (for full list see section 7.1). Each sachet of **normast®** micro granules contains 400,00 mg of a mixture of excipients (for full list see section7.1).

3) **PHARMACEUTICAL FORM**
Oblong white color, tablets. White color granulates.

4) **CLINICAL PARTICULARS**

4.1) **Indications.** Palmitoylethanolamide is nutritional factor acting in the body promoting the control of the physiologic tissue reactivity also in presence of a high oxidative stress. Thus, it is intended to be used under medical supervision in the dietary regimen of those subjects affected by disorders sustained by tissue mast cell hyper-reactivity. In these subjects, it appears useful a physiological intervention to counteract the endogenous production deficit of Palmitoylethanolamide, when recurrent inflammatory conditions compromise their endogenous biosynthetic rate.

4.2) **Posology and direction for use.** According to medical indications, **normast®** tablets indicatively 1-2 tablet/day; Normast micro granules 1-2 sachet/day to be placed directly under the tongue, letting dissolve them upon contact with saliva.

4.3) **Contraindications.** None

4.4) **Warning and Precautions for use**. The product is not to be used as the sole source of nutrition. Keep away from the reach of children under 3 years of age.

4.5) **Interactions**. Not demonstrated.

4.6) **Pregnancy**. The product administration is not recommended during pregnancy due to insufficient data regarding the use of Palmitoylethanolamide in similar conditions.

4.7) **Effects on ability to drive and use machines.** Palmitoylethanolamide, at the recommended dosage, does not affect the ability to drive a car or operate machinery.

4.8) **Undesirable effects**. No side effects have been reported up to now, even after a long term administration with high dosage. No cases of addiction or drug dependence have been reported.

4.9) **Overdose**. Up to now no clinical cases of overdose have been reported.

5) **PHARMACOLOGICAL PROPERTIES.**
Classification: Food for Special Medical Purposes

5.1) **Pharmacodynamic properties.**Palmitoylethanolamide is an endogenous n-acylethanolamine, chemically similar to the endocannabinoid anandamide with a biological activity spectrum largely common. The main difference between these two molecules concerns the inability of Palmitoylethanolamide to interact with the CB1 receptor, responsible for the psychotropic effects of endocannabinoid, thus its intake is not associated to these central effects. Palmitoylethanolamide has anti-inflammatory effects, concerning the peripheral inflammatory processes and the central neuroinflammation, and analgesic effects, which are evident both in acute and chronic-neuropathic pain conditions, and highlighted by several clinical trials in vitro and in vivo and by an increasing number of clinical trials.

5.2) **Mechanisms of action.** More mechanisms of action of Palmitoylethanolamide have been described, featuring under various pathological conditions. Two main cell targets of the molecule are known: mast cell and microglia. The main effect of Palmitoylethanolamide is the normalization of the excessive activation of these immunocompetent cells, involved in peripheral inflammatory processes, central neuroinflammation and acute and chronic-neuropathic pain processes. At a molecular level, Palmitoylethanolamide interacts with several receptors; the main one is the nuclear PPAR-α receptor concerned in the control of inflammatory and neuro-protective processes. In certain conditions, Palmitoylethanolamide interacts with the Cannabinoid receptor CB2 that is present mainly on the immune cells, including mast cell and microglia, whose expression highly increases when inflammatory conditions and neuroinflammation associated to neurodegenerative disorders occur. Palmitoylethanolamide potentiates the activity of the endogenous acyl-ethyl-amides. The so called entourage effect mechanism, allows Palmitoylethanolamide to indirectly interact with the endocannabinoid and endovanillinoid systems. Clinical efficacy. The use of Palmitoylethanolamide in the clinical practice has shown to improve clinical symptoms, including pain and functionality, manifesting in many diseases of inflammatory, traumatic and neurodegenerative type and affecting both Central and Peripheral Nervous Systems.

5.3) **Pharmacokinetic**. The Palmitoylethanolamide time profile in human plasma, following oral administration of a single dose ranging from 300 and 1200mg, shows a dose-dependent increase of Palmitoylethanolamide concentration. The peak plasma level of Palmitoylethanolamide is observed 1 hour after the intake; then plasma level decreases returning to basal value within 6 hours. After 1 hour, Palmitoylethanolamide plasma levels become about the double of basal ones after the intake of a 300mg tablet, while increase seven times after the intake of 1200mg. Trials studies have shown that after oral administration, Palmitoylethanolamide spreads equally over all the tissues; a small percentage of the molecule passes across the hemato-encephalic barrier, reaching the brain tissues.

6) **TOXICOLOGY AND TOLERABILITY.** Toxicology studies have shown that the LD/50 of Palmitoylethanolamide administered via intraperitoneal injection in the dog is higher than 400 mg/kg and after single administration in the mice, through gastric probe, exceeds 5000 mg/kg, while after repeated administrations through gastric probe exceeds 500/mg/kg/day.
Clinical trials conducted on a considerable number of patients, showed the optimal tolerability of the Palmitoylethanolamide also at high dosages and the lack of clinically relevant variations in the hematological and hemato-chemical examinations performed.

6.1) **Palmitoylethanolamide and embriotoxicity.** No teratogenic or embriotoxic effects of Palmitoylethanolamide (PEA) have been observed after administration of 50 mg/kg of weight during pregnancy for a period of 12 days. Moreover, the newborns whose mothers have received PEA before giving birth, 10 days after delivery were more resistant to the Shigella Shigae toxin. Similarly, newborns whose mothers have been receiving PEA before delivery, have shown an increasing resistance evident already 5 days after birth: these data suggest that the mother might have transferred PEA to newborns through mother's milk.

6.2) **Palmitoylethanolamide and mutagenicity.** Though it can be excluded a potential mutagenic effect of Palmitoylethanolamide because of its presence in mammalians, PEA's mutagenicity has been verified by Amest test using 5 different species of S. Typhimurium (TA 1535-TA 1537- Ta 1538- TA 98 and TA 100). With Ames test, PEA at dosages ranging between 10.000 and 1.000 µg/ml has not significantly modified the revertant numbers.

6.3) **Palmitoylethanolamide gastric tolerability.** Oral administration of a 50 mg/kg dose of Palmitoylethanolamide in mice (a dose approximately 5-times higher when compared with the effective dose) and of 10 mg/kg dose in repeated administrations for 5 days, do not induce ulcers formation. When administered at 50 mg/kg dose simultaneously with 15 mg/kg diclofenac, dosage known to induce gastric lesions, PEA decreases the ulcerogenic potential of FANs, significantly reducing the number of animals developing ulcerations and mitigating the possible damage.

7) **PHARMACEUTICAL PARTICULARS**

7.1) **Excipients**. A single tablet of normast® 300mg and 600mg contain respectively 141,47 mg and 282,94 mg of a mixture of excipients (microcrystalline Cellulose, Sodium croscarmellose, Povidone, Magnesium stearate, Colloidal silica, anhydrous Polysorbate 80). Each sachet of normast® microgranules contains 400.00mg of a mixture of excipients (Sorbitol, Polysorbate 80, Sucrose Palmitate).

7.2) **Incompatibilities.** Not known.

7.3) **Shelf life.** 3 years.

7.4) **Special precautions for storage.** This product does not require any particular storage condition.

7.5) **Nature and contents of container.** Blister of aluminium foil and white color PVC/PVDC packed in cartons containing 20 or 30 tablets. Thermo welded paper/Alum/PE sachet packed in cartons containing 20 or 10 sachets.

7.6) **Special precautions for disposal.** No special instructions needed.

8) **MARKETING AUTHORIZATION HOLDER**
Epitech Group Srl - Via Egadi, 7 – 20144 Milan – Italy

9) **MARKETING AUTHORIZATION NUMBER(S)**

normast®	300mg tablets	DGSAN 600.12/D 3955/27917
normast®	600mg tablets	DGSAN 0028029-P
normast®	600mg Microgranules	DGSAN 0003456-P

10) **DATE OF FIRST AUTHORIATION/RENEWAL OF THE AUTHORIZATION**

normast®	300mg tablets	31/07/2006
normast®	600mg tablets	30/09/2008
normast®	600mg Microgranules	11/02/2010

11) **DATE OF TEXT REVISION** 06/2013

Retail price

normast®	pack with 30 tablets 300mg each	€ 20,00
normast®	pack with 20 tablets 600mg each	€ 28,00
normast®	Microgranules pack with 20 sachets 600mg each	€ 31,00
normast®	Microgranules pack with 10 sachets 600mg each	€ 18,00