SUMMARY OF THE PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Anervan Novum film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
1 tablet contains: Ergotamine tartrate 0,5 mg, chlorcyclizine hydrochloride 10 mg and caffeine 50 mg.

For complete list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
Film-coated tablet
White to yellow, dotted, round, biconvex, diameter 10,5 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Treatment of incipient attacks of migraine.

4.2 Posology and method of administration
Adults: 1-2 tablets at the first reliable signs of an incipient attack. If needed, the dose can be repeated after half an hour. Generally, an effect is obtained by 1-2 mg ergotamine given early during the attack. The total dose per attack should not exceed 2 mg ergotamine. When an adequate dose has been found, at later attacks, the whole dose should be taken as early as possible, preferably at one occasion at the onset of the attack.

Where the periodicity of the attacks makes prophylactic treatment possible during single days, for example at monthly attacks in connection with menstruation or periods of nightly attacks of Hortons disease, treatment can be given before an expected attack.

If nausea and vomiting occur, treatment with suppositories are preferred.

Children from 10 years and adolescents: Generally half the adult dose.

4.3 Contraindications
Hypersensitivity to ergot alkaloids, caffeine, chlorcyclizine hydrochloride or to any of the excipients.
Anervan Novum should not be given within 6 hours after intake of sumatriptan or other 5H1 receptor agonists with exemption of eleptriptan, where an interval of 24 hours is needed.
Accordingly, sumatriptan or other 5H1 receptor agonists should not be given within 24 hours after intake of Anervan Novum.
Concomitant treatment with ergotamine and inhibitors of the enzyme group CYP3A such as macrolide antibiotics (for example erythromycin, telitromycin), protease inhibitors (for example ritonavir, indinavir, nelfinavir) or azole antimycotics (for example ketoconazole, itraconazole) (see 4.5).
Concomitant treatment with vasoconstrictors such as ergot alkaloids, sumatriptan and other 5HT1-receptor agonists as well as nicotine (see 4.5).
Pregnancy and breast feeding (see 4.6).
Impaired peripheral circulation, obliterative vascular disease, coronary heart disease (especially in instable angina or spasm angina), untreated hypertension, septic conditions, shock.
Temporalis arteritis.
Hemiphlegic migraine, basilaris migraine.
 Pronounced impaired renal- or hepatic function.

4.4 Special warnings and special precautions for use
Anervan Novum should not be used daily. If daily prophylaxis is needed, an ergotamine product should not be used.
The use of ergotamine containing drugs such as Anervan Novum in higher doses and during a longer period of time than what is recommended should be avoided. Long term use of high doses can cause vasospastic reactions and fibrinolytic changes, especially of pleura and retro peritoneum.

The patient should be informed that the following symptoms are those that first occur after doses exceeding the maximal dose: hyperesthesia and parenthesis (for example numbness, itching) of fingers and toes, non-migraine related nausea and vomiting, symptoms of cardiac ischemia. If symptoms of peripheral vasoconstriction or cardiac ischemia occur, treatment should be stopped immediately, a physician should be consulted and treatment with a vasodilator should be considered (see section 4.9). Also in patients who have not had any coronary heart disease earlier, ergotamine, because of its constringent effect on the blood vessels, can cause myocardial ischemia and in rare cases, a myocardial infarct.

Patients with mild to moderate impairment of the liver function, especially cholestasis, should be carefully followed in order to avoid over exposure because of impaired metabolism of the drug.

Long-term treatment with painkillers against headache can increase the headache. If this situation is known or suspected, a medical advice should be given and the treatment should be stopped. The diagnosis headache because of drug over use should be suspected in patients with frequent or daily headache in spite of (or because of) regularly use of drugs against headache.
Drug induced headache has been reported after long term and daily use of Anervan Novum.

4.5 Interaction with other medicinal products and other forms of interaction
Ergotamine
Concomitant treatment with ergotamine and inhibitors of the enzyme group CYP3A such as macrolide antibiotics (for example erythromycin, telitromycin), protease inhibitors (for example ritonavir, indinavir, nelfinavir) orazole antimycotics (for example ketoconazole, itraconazole) are contraindicated (see 4.3), since this can lead to an elevated level of ergotamine and thus cause ergotamine toxicity (vasospasm and ischemia of extremities and other tissues).
Concomitant use of vasoconstrictors such as ergot alkaloids, sumatriptan and other 5HT1-receptor agonists as well as nicotine must be avoided, since this can lead to increased vasoconstriction (see 4.3). Caution concerning dosage interval should be taken at intake of
ergotamine after treatment with 5HT1-receptor agonists and the reverse, at intake of 5HT1-receptor agonists after ergotamine intake (see 4.3). The combination with beta-blockers and ergotamine is generally well tolerated, but caution is demanded in patients with impaired peripheral circulation.

**Caffeine**
Caffeine is an adenosine antagonist and can be expected to increase the effective dose of adenosine. The combination should therefore be avoided.
Caffeine is metabolised mainly by the enzyme CYP1A2, and an inhibitor of CYP1A2 (for example fluvoxamine) causes elevated plasma concentrations of caffeine.
Caffeine causes elevated plasma concentrations of clozapine, probably by inhibiting the CYP1A2-mediated metabolism of clozapine.
Caffeine causes decreased plasma concentrations of lithium.

**Chlorcyclizine**
There are no known interactions.

### 4.6 Pregnancy and lactation

**Pregnancy**
Ergotamine has a uterus contracting effect and can therefore induce abortion or hypertonic labour. Anervan Novum is therefore contraindicated during pregnancy.

**Breast-feeding**
Ergotamine enters breast milk in such quantities that a risk for an effect on the child can be expected even with therapeutic doses. Anervan Novum is contraindicated in breast-feeding women. Caffeine enters breast milk but a risk for the child is not expected with therapeutic doses. There is no information regarding the entrance of chlorcyclizine into breast milk.

### 4.7 Effects on ability to drive and use machines

Patients who experience vertigo during treatment with Anervan Novum should not drive or use machines.

### 4.8 Undesirable effects

The most frequently reported undesirable effects are nausea and vomiting. Depending on the size of the ergotamine dose, signs of vaso constriction can occur.

**Frequencies:** Very common: >1/10, Common: >1/100, <1/10, Uncommon: >1/1000, <1/100, Rare: >1/10 000, <1/1000; Very rare: <1/10 000.

**General symptoms and/or symptoms at the site of administration**

**Less common:** Cyanosis.
**Rare:** Headache.

**Respiratory tract system, chest and mediastinum**

**Rare:** Allergic reactions (dyspnoea).

**Blood vessels**
Less common: Angina pectoris, peripheral vaso constriction (especially in the lower extremities).
Rare: Hypertension.
Very rare: Gangrene.

Central and peripheral nervous system
Common: Vertigo.
Less common: Paresthesia and hypesthesia of fingers and toes.

Coronary
Rare: Bradycardia, tachycardia, myocardial ischemia, myocardial infarction.

Skin and subcutaneous tissue
Rare: Allergic reactions (such as rash, face edema, urticaria).

Gastrointestinal system
Less common: Nausea, vomiting.
Rare: Colic, diarrhoea.

Musculoskeletal system and connective tissue
Rare: Myalgia.

Injuries and poisoning and treatment complications
Rare: Ergotism (strong arterial vaso constriction with symptoms of peripheral vascular ischemia).

Ears and vestibular system
Rare: Vertigo.

In single patients who have taken ergotamine regularly during several years, fibrinolytic changes have been observed, mainly of the pleura and retro peritoneum, but also single cases of fibrinolytic changes of cardiac valves have been reported (see also section 4.4).

4.9 Overdose

Symptoms
Ergotamine: The main risk is vascular spasm (increased risk if the patient is already using ergotamine) and CNS effects. Vascular spasm of the extremities: Peripheral coldness, pains, paleness, cyanosis, pulse-lessness, risk for thrombosis and gangrene. Paresthesia, flexion contracture, muscle cramp, tremor. Spasm in other arteries can give angina pectoris, effects on vision, lumbago, abdominal pain, intestine gangrene, kidney effects, tongue necrosis. Uterus bleeding, abortion. Nausea, vomiting, diarrhoea. Mydriasis, mouth dryness. At acute, massive intoxication, hypertension or hypotension, bradycardia or tachycardia, heart failure, arrhythmias, excitation, dizziness, hallucinosis, cramps, coma, brain edema. Respiratory depression, bronchospasm. Hyper or hypo pyrexia. Liver and kidney effects.

Caffeine: Nausea, headache, vertigo, anxiety, tinnitus, tremor, excitation, tachycardia, tachypnoea, increased urinary volumes. After larger doses, vomiting (eventual hematemesis), hyperthermia, hyperventilation, hyperaemia, hyponatremia, ventricular extra systoles, hypertension, hallucinations, eventual delirium and seizures (even status epilepticus). After massive doses, respiratory depression, ventricular tachycardia, cardiac fibrillation, myocardial
infarction and circulatory collapse. Rhabdomyolysis and kidney failure. ARDS (adult respiratory distress syndrome) in single cases.

Treatment
Ergotamine: If indicated, gastric emptying, charcoal. In general impairment, treatment in a respirator on a wide indication. Diazepam against seizures. Atropine against nausea, bowel cramps, bradycardia. Lidocaine in case of cardiac arrhythmias. Calcium glubionate (9 mg Ca/ml) 10 ml intravenously against muscle pains. At signs of vascular spasm: Dextran 500-1000 ml the first 24 hours, later 500 ml/24 hours. Hydrocortisone, initially 300 mg intramuscularly or intravenously. Glyceryl nitrate 0,5 mg sublingually, to be repeated if needed every 10 minutes. In case of good, but short acting, effect, sustained release nitroglycerine. In case of severe vascular spasm with risk of gangrene: Glyceryl nitrate, initially 0,5 microgram/kg/minute intravenously and then an increase of the dose with 0,5 microgram/kg/ minute every 5-10 minutes until an effect is reached. Treatment with glyceryl nitrate can be gradually withdrawn during 12-24 hours. If needed, captopril 50 mg x 3 orally, can be added. In case of signs of hypercoagulability heparin is added (10-15000 IE/day to an adult). Nota bene that dextran should not be given in that case.

Caffeine: If indicated, gastric emptying, charcoal. Diazepam in case of CNS excitation and seizures. In case of tachycardia and hypertension, a beta blocker (for example metoprolol) can be given. In case of persisting hypertension, eventually fentolamine 2,5 – 5 mg (children 0,05-0,1 mg/kg) intravenously every 5 minutes as needed, thereafter eventually as an infusion. In case of circulatory collapse, fluid intravenously and inotropic support. Antacids if needed in combination with omeprazol 40 mg intravenously to an adult in case of hematemesis. Good diuresis should be achieved. Symptomatic treatment. In case of very severe poisoning, eventually hemoperfusion.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Anti migraine agents. ATC-code: N02C A72
Ergotamine has a vascular constrictor effect and since long it has been used against various types of vascular headache. Caffeine enhances the absorption of ergotamine. Chlorcyclizine counteracts nausea.

5.2 Pharmacokinetic properties
Ergotamine
Ergotamine is absorbed to a minor extent from the gastrointestinal tract, and the absorption is probably even more decreased by the intestinal stasis during a migraine attack. Ergotamine is subject to a first pass metabolism. Caffeine is included in the formulation in order to increase the bioavailability, even if the mechanism is not evident. The plasma protein binding is approx. 93-98%. Ergotamine or its metabolites have been detected in breast milk. Ergotamine is metabolised to a great extent in the liver via the enzyme CYP3A4, and the main part of the metabolites are excreted via the bile. Approx. 4% of the dose is excreted in the urine. Certain metabolites are pharmacologically active. The elimination of ergotamine is biphasic, with half-lives of approx. 2 and 21 hours, respectively.
**Caffeine**
Caffeine is absorbed to a great extent after oral administration. The distribution is extensive, among other into the CNS, saliva, breast milk and placenta. Caffeine is almost completely metabolised in the liver via oxidation, demethylation and acetylation. Caffeine is excreted in the urine as metabolites and only approx. 1% in the unchanged form. The half-life is approx. 3-7 hours.

**Chlorcyclizine**
Information is missing.

### 5.3 Preclinical safety data
There is no preclinical information judged to be of importance for the clinical security more than the information that is given in other sections of the summary of product characteristics.

### 6 Pharmaceutical particulars

#### 6.1 List of excipients
Tablet core:
Ascorbic acid, tartaric acid, magnesium stearate, anhydrous colloidal silica dioxide, microcrystalline cellulose, crospovidone.

Film coating:
Talc, magnesium stearate, macrogol, basic butylated methacrylate copolymer, vanillin aroma, titanium dioxide (colour E 171).

#### 6.2 Incompatibilities
Not applicable.

#### 6.3 Shelf-life
2 years.

#### 6.4 Special precautions for storage
No special precautions.

#### 6.5 Nature and content of container
PVC/PVDC/Al blister.
30 and 100 tablets.

#### 6.6 Instructions for use and handling, and disposal (if appropriate)
No special instructions.

### 7 Marketing authorisation holder
C.G. Papaloisou Ltd

### 8 Marketing authorisation number(s)
S00499
9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

22/02/2010

10 DATE OF REVISION OF THE TEXT

14/10/2011