Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

Grippostad®C capsules, hard

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 capsule, hard contains 200 mg paracetamol, 150 mg ascorbic acid, 25 mg caffeine, 2.5 mg chlorphenamine hydrogen maleate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsule, hard

Capsule top: yellow opaque
Capsule bottom: white opaque, filled with white to yellowish powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications
Symptomatic treatment of common cold-related concurrently occurring symptoms such as headache and pain in limbs, rhinitis and dry cough.Grippostad®C reducesconcomitantly occurring fever or increased body temperature.

Because of the fixed combination, doses of the single substances of Grippostad® C cannot be adjusted individually in cases where one of the mentioned symptoms occurs predominantly. In these cases medicinal products with different compositions should be preferred.

4.2 Posology and method of administration
Adults and adolescents aged 12 years and overtake 2 capsules three times a day.

Patients with hepatic and/or renal impairment
Dose must be reduced or dosing interval must be prolonged in patients with impaired hepatic or renal function and Gilbert's syndrome.
Grippostad®C must not be used with severe liver and/or kidney insufficiency (see section 4.3).

Method and duration of administration
The capsules are swallowed with a sufficient amount of fluid.

Grippostad®C should not be used over long periods of time or at high dosages without

consulting a doctor.

4.3 Contraindications
- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1
- Severely impaired kidney function
- Children under 12 years of age
- Pregnancy
- Breast-feeding

4.4 Special warnings and precautions for use
Grippostad®C should only be used with special caution or after consulting a doctor with
- Impaired renal function
- Impaired hepatic function
- Gilbert's syndrome
- Oxalate urolithiasis
- Iron storage diseases (thalassemia, haemochromatosis, sideroblastic anaemia)
- Chronic alcohol abuse
- Pyloroduodenal obstruction and bladder outlet obstruction
- Narrow-angle glaucoma
- Ventricular or duodenal ulcers
- Hyperthyroidism
- Cardiac arrhythmias (risk of enhancing tachycardia and extra systoles)
- Anxiety disorders (risk of enhancement).

With high fever, signs of a secondary infection, exacerbation of symptoms or further complications a doctor must be consulted.

In general, paracetamol-containing medicines should only be used for a few days and not in higher doses without a doctor’s or dentist’s advice.

Prolonged use of high doses of analgesicsat variance with their intended use may produce headaches, which must not be treated with increased doses of these medicines.

Warnings
Paracetamol
As with all paracetamol-containing medicines exceeding the recommended dose can lead to severe liver damages. In this case immediate treatment is necessary.

To avoid risk of overdosing, it has to also be made sure that in use of further paracetamol-containing medicines the maximum daily dose of paracetamol (from43 kg body weight: 4000 mg paracetamol) is not exceeded.

Ascorbic acid
In isolated cases patients with congenital glucose-6-phosphate dehydrogenase deficiency experienced in part severe haemolytic anaemia after use of high doses (4 g daily) of ascorbic acid. Exceeding the recommended dose must therefore be avoided.

There is a risk for the formation of calciumoxalate stones after use of high doses of ascorbic acid in patients predisposed for kidney stone formation.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take Grippostad®C.

4.5 Interactions with other medicinal products and other forms of interactions
The following interactions are known for the individual substances of Grippostad®C:

Paracetamol
- Concurrent use of medicines that lead to a deceleration ofgastric emptying, such as propantheline, may lead to delaythe absorption and onset of action of paracetamol
- Concurrent use of medicines that lead to acceleration of gastric emptying, such as metoclopramide, can cause an acceleration of absorption and onset of action of paracetamol.
- Concomitant use of AZT (zidovudine) may increase the tendency for developing neutropenia. Grippostad®C should, therefore, only be used concurrently with AZT on doctor's advice.
- Use of probenecid inhibits binding of paracetamol to glucuronic acid and thereby leads to reduction of paracetamol clearance of approximately factor 2. In concurrent use with probenecide the paracetamol dose should be reduced.
- Salicylamide may prolong elimination half-life of paracetamol.
- Special caution is necessary in concurrent use of drugs causing enzyme induction as well as potentially hepatotoxic substances (see section4.9).
- Repeated use of paracetamol over several weeks increases the effect of anticoagulants. The occasional use of paracetamol has no significant effect.
- Cholestyramine reducesthe absorption of paracetamol.

Chlorphenamine maleate
Concurrent use of chlorphenamine maleate with central depressant drugs or alcohol potentiates the sedating effect.

Caffeine
- Caffeine may weaken the sedating effect of different substances such as e.g. barbiturates, antihistamines etc.
- Caffeine works synergistically on tachycardiac effect of e.g. sympathomimetics, thyroxin etc.
- In concurrent use of theophylline the elimination of theophylline may be reduced.
- Caffeine increases the addictive potential of ephedrine-type substances.
- The combination of caffeine and substances with a broad spectrum of activity (e.g. benzodiazepines) may individually cause different and unpredictable interactions.
- Oral contraceptives, cimetidine and disulfiram reduce caffeine breakdown in the liver; barbiturates and nicotine accelerate it.
- Concomitant administration of quinolone carboxylic acid-type gyrase inhibitors may reduce elimination of caffeine and its metabolite paraxanthine.

Ascorbic acid

So far there are no known interactions.

4.6 Fertility, pregnancy and lactation

Pregnancy

Use of Grippostad®C is contraindicated during pregnancy, because epidemiologic studies indicate that chlorphenamine maleate increases the risk for CNS or cranial anomalies and tumors in childhood. Results from one study also indicate an increased risk for retrolental fibroplasia in premature infants after antihistamine exposition in the last two weeks before delivery.

Breast-feeding

Because it is unknown, if chlorphenamine maleate is excreted in breast milk, nursing must be stopped during Grippostad®C treatment.

4.7 Effects on ability to drive and use machines

Even when used as directed, this medicine may alter alertness to such an extent that the ability to actively participate in road traffic or to operate machines is impaired. This applies especially in combination with alcohol.

4.8 Undesirable effects

In this section frequencies of undesirable effects are defined 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 (frequency cannot be estimated from the available data).

Investigations

Not known: Use of paracetamol may influence uric acid determination by phosphotungstic acid and blood glucose level determination using glucose oxidase peroxidase.
After administration of gram doses of ascorbic acid the ascorbic acid urine concentration can increase to such an extent that evaluation of different clinical-chemical parameters (glucose, uric acid, creatinine, inorganic phosphate) can be disturbed. Also, use of gram doses can lead to false negative results in trying to find evidence of occult blood in the faeces. In general, chemical evidence methods based on color reactions can be impaired.
The reaction of cutaneous allergy tests may be reduced by chlorphenamine maleate.

Cardiac disorders

Not known: Cardiac arrhythmias such as e.g. tachycardia.

Blood and lymphatic system disorders

Very rare: Changes in blood picture such as leukopenia, neutropenia, agranulocytosis, thrombocytopenia, thrombocytopenic purpura, pancytopenia, aplastic anaemia and at high dosage light methaemoglobin formation.

Nervous system disorders

Very rare: Dyskinesia.
Not known: Sedation, drowsiness.

Eye disorders

Very rare: Triggering of glaucoma (narrow-angle glaucoma), visual disorders.

Respiratory, thoracic and mediastinal disorders
Very rare: Respiratory hypersensitivity, paracetamol may trigger bronchospasm (analgesic asthma) in predisposed persons.

Gastrointestinal disorders
Common: Dry mouth.
Very rare: Gastrointestinal complaints.

Renal and urinary disorders
Very rare: Micturition disorders. After prolonged use of higher doses kidney damages may occur.

Skin and subcutaneous tissue disorders
Uncommon: Allergic skin reactions (erythematous or urticarial) possibly accompanied by rise in temperature (drug fever) and mucosal lesions.

Very rare cases of serious skin reactions have been reported.

Metabolism and nutrition disorders
Very rare: Increase in appetite

Immune system disorders
Very rare: For the active substance paracetamol severe hypersensitivity reactions (angiooedema, dyspnoea, sweating, nausea, hypotension extending to circulatory failure and anaphylactic shock) have been described.
Not known: Bullous skin reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis/Lyell's syndrome were observed in isolated cases in temporal relationship with the use of Grippostad®C.

Hepatobiliary disorders
Rare: Increase of liver transaminases.
Very rare: Liver damages may occur after prolonged used of higher doses or after overdosing.

Psychiatric disorders
Very rare: Psychotic reactions.
Not known: Internal restlessness, insomnia.

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
Bundesinstitut für Arzneimittel und Medizinprodukte
Dept. Pharmakovigilanz
Kurt-Georg-Kiesinger-Allee 3
D-53175 Bonn, Germany

Website: www.bfarm.de

4.9 Overdose

Symptoms of intoxication

So far overdosing with Grippostad®C is unknown.

The symptoms of overdosing of Grippostad®C are compiled of the symptoms of intoxication of each individual substance.

Paracetamol

Risk for intoxication is especially high in elderly patients, small children, patients with liver diseases, chronic alcohol abuse, chronic malnutrition and concurrent use of medicines that lead to enzyme induction. In these cases overdosing may lead to death.

As a rule, symptoms occur within 24 hours and may include: Nausea, vomiting, anorexia, paleness and abdominal pains; followed by a subjective improvement in overall well-being, although mild abdominal pain remains as indication of liver damage.

An overdose with approximately 6 g or more of paracetamol asa single dose in adults or of 140 mg/kg body weight in children leads to liver cell necrosis, which could lead to a totally irreversible necrosis and later to hepatocellular insufficiency, metabolic acidosis and encephalopathy. These again could lead to coma, also with death as a result. At the same time elevated concentrations of transaminases (AST, ALT), lactate dehydrogenase and of bilirubin in combination with an increased thromboplastin time were observed, which can occur after 12-48 hours of use. Clinical symptoms of liver damage become apparent after 2 days and reach a peak after 4-6 days.

Acute renal failure and necrosis of the renal tubules can occur, even if there are no serious liver damages. Other not liver-related symptoms that were observed after a paracetamol overdose are myocardial anomalies and pancreatitis.

Chlorphenamine maleate

Overdose may lead to an anticholinergic syndrome with flushing of the face, ataxia, agitation, hallucinations, muscle tremor, convulsions, fixed dilated pupils, dry mouth, constipation and abnormally high fever. Further, central nervous signs of intoxication (hallucinations, impaired co-ordination or convulsions) may occur. Final symptoms are coma, respiratory arrest und cardiovascular collapse.

Caffeine

With the intake of 1 g caffeine or more, within a short period of time, symptoms of intoxication may occur: Tremor, CNS symptoms, cardiovascular reactions (tachycardia, myocardial damages).

Ascorbic acid

For the risk of haemolysis and kidney stones (see section 4.4). Transient osmotic diarrhoea accompanied by the usual abdominal symptoms may occur uncommonly after the use of single doses of more than 3 g, after the use of 10 g they occur almost always.

Treatment of intoxication
Treatment of an overdose is performed symptomatically.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Cold combination preparations, paracetamol, combinations
ATC code: R05XA01

Paracetamol
Paracetamol has an analgesic, antipyretic and very weak antiphlogistic effect. The mode of action of paracetamol is not entirely clear. Proven is a significant inhibition ofthe cerebral prostaglandin biosynthesis, while the peripheral prostaglandin biosynthesis is only weakly inhibited. Furthermore paracetamol inhibits the effects of endogenous pyrogens on the hypothalamic temperature-regulation centre.

Chlorphenaminemaleate
Chlorphenamine is a classical H_1-antihistamine, which suppresses histamine effects arising in the course of immune reactions. In the context of an influenza-like infection, this includes increased capillary permeability in the vicinity of the venules, and constrictor effects on smooth muscle, particularly bronchial muscle. Relief of swelling of the nasal mucosa and a reduction in mucus production restore the capacity for nasal breathing.

Caffeine
Caffeine is a xanthine derivative and increases the analgesic properties of paracetamol.

Ascorbic acid
Ascorbic acid is an essential substance for man. Ascorbic acid and dehydroascorbic acid, formed from ascorbic acid in the organism, form a redoxsystem of high physiological importance.

Because of its redox potential ascorbic acid works as co-factor of many enzyme systems (collagenisation, catecholamine synthesis, hydroxylation of steroids, tyrosine and body foreign substances, biosynthesis of carnitine, regeneration of tetrahydrofolic acid as well as alpha amidation of peptides, e.g. ACTH and gastrin).

Furthermore, ascorbic acid deficiencyimpairs immune defence reactions,especially chemotaxis, complement activation and interferon production. Not all molecular biological functions are as yet completely clear.

Ascorbic acid improves absorption of iron salts by reducing ferric ions and formation of iron chelates. It blocks the chain reaction, triggered by the oxygen radicals in aqueous body compartments.The antioxidative functions relate in close biochemical interaction to those of vitamin E, vitamin A and carotinoids. A reduction of potentiallycarcinogenic substancesin the gastrointestinal tract by ascorbic acid is not yet sufficiently proven.

5.2 Pharmacokinetic properties

Paracetamol

Absorption

Oral paracetamol is rapidly and completely absorbed. Peak plasma concentrations are attained after 30-60 minutes after intake.

Distribution

Paracetamol is rapidly distributed in all tissues. Blood, plasma and saliva concentrations are comparable. Plasma protein binding is low.

Biotransformation

Paracetamol is mainly metabolised in the liver by ways of conjugation of glucuronic acid and sulfuric acid.At doses that exceed the therapeutic dose, the latter routeis quickly saturated.A small part of the metabolism takes place through the catalyst cytochrome P 450 (mainly CYP2E1) and leads to the formation of the metabolite N-acetyl-p-benzoquinonimine, which normally is quickly detoxified by glutathioneand bound by cysteine and mercapturic acid. In case of massive intoxication the amount of this toxic metabolite is increased.

Elimination

The excretion is mainly performed through urine. 90% of the absorbed amountis eliminated within 24 hours mainly as glucuronides (60-80%) and sulfate conjugate (20-30%) via the kidneys.Less than5% are excreted unchanged. Elimination half-life is approximately two hours. In patients with liver and renal function impairment, after overdosage as well as in newborn babies half-life is prolonged.The maximum effect and the average duration of action (4-6 hours) correlate approximately with the plasma concentration.

Renal impairment

Elimination of paracetamol and its metabolites is delayed in patients with severe renal insufficiency (creatinine clearance < 10 ml/min).

Older people

The ability for conjugation is unchanged.

Chlorphenaminemaleate

Peak blood chlorphenamine levels are attained 1-2 hours after administration. The duration of action of chlorphenamine is 3-6 hours. The breakdown occurs mainly in the liver by hydroxylation and conjugation, but also by demethylation and the formation of N- and S-oxides.

Bioavailability after oral administration is 25-50% due to the high *first-pass* effect, which is reduced in hepatic insufficiency. Plasma protein binding is 69-72%. The fictional volume of distribution of 3-7 l per kg body weight is relatively high. Plasma half-life of chlorphenamine maleate in adults is 15-36 h, inchildren 10-13 h. In kidney insufficiency prolongation of the half-life of the metabolites must be expected. In urine 0-34% according to the pH level (alkaline to acidic) of the dose are eliminated as unchanged chlorphenamine. Accumulation can occur after prolonged administration.

Caffeine

After oral application caffeine is absorbed rapidly and nearly completely ($t_{1/2}$= 2-13 minutes) and is nearly completely bioavailable. After intake of 5 mg/kg C_{max} was attained within 30-40 minutes. Plasma protein binding varies from 30 to 40% and volume of distribution is 0.52-1.06 l/kg. Caffeine is distributed in all compartments and rapidly crosses the blood-brain and placental barrier and is excreted in breast milk.

Plasma half-life lies between 4.1 and 5.7 hours, whereby intra- and interindividual fluctuations have lead to values of up to 9 or 10 hours.

Caffeine and its metabolites are mainly excreted renally. In urine, collected for 48 hours, 86% of the applied dose was found, of which only a maximum of 1.8% were unchanged caffeine. The main metabolites are 1-methyl uric acid (12-38%), 1 methylxanthine (8-19%) and 5-acetylamino-6-amino-3-methyl-uracil (15%). The faeces contained only 2-5% of dose. 1.7-dimethyl uric acid was identified as the main metabolite, constituting 44% of the total amount.

Ascorbic acid

Ascorbic acid is absorbed from the proximal intestine depending in a concentration dependent manner. With increasing single dose the bioavailability decreases to 60-75% after 1 g, to approx. 40% after 3 g to as low as 16% after 12 g. The unabsorbed part is broken down by the colonic mucosa mainly into CO_2 and organic acid.

In healthy adults the maximum metabolic turnover of 40 to 50 mg/day is reached with plasma concentrations of 0.8-1.0 mg/dl. The total daily turnover lies in the vicinity of 1 mg/kg body weight. After extremely high oral dosing short-term plasma concentrations of 4.2 mg/dl are attainable after 3 hours.

In these conditions 80% ofunchanged ascorbic acid is eliminated in urine.The mean half-life is 2.9 hours. Renal elimination is by glomerular filtration, followed by reabsorption into the proximal tubule. Upper border concentrations of ascorbic acid/dl plasma in healthy adults are 1.34±0.21 mg in men and 1.46±0.22 mg in women.

The body pool of ascorbic acid is after high application of about180 mg/d at least 1.5 g. Accumulation of ascorbic acid occurs in pituitary gland, adrenal gland, optic lens and leukocytes.

5.3 Preclinical safety data

Acute and chronic toxicity

Paracetamol

Animal studies on acute, subchronic and chronic toxicity of paracetamol in rats and mice revealed gastrointestinal lesions, blood dyscrasias, degenerations of the liver and kidney parenchyma to the point of necrosis. The cause of these changes is thought to be due in some part to the mechanism of action of paracetamol (see above) and in some part to its biotransformation. The metabolites implicated in causing the toxic effects and the resultant organ alterations have also been documented in humans. Paracetamol, therefore, should not be used for prolonged periods of time and/or in high doses.

Cases of reversible, chronic aggressive hepatitis have been described for daily doses of 3.9 g and 2.9 g and treatment duration of 1 year. Daily oral doses with significant liver damaging effect in non-alcoholics are in the rangeof 5.8 g, whereby symptoms of intoxication may occure as early as 3 weeks after intake.

Chlorphenamine maleate
After oral administration of chlorphenamine maleate the LD_{50} in mice is 162 mg per kg body weight.
Studies on chronic toxicity revealed no evidence of substance specific toxic effects.

Caffeine
In animal experiments caffeine causes gastrointestinal ulcers, liver and kidney damages after long-term administration of therapeutically not significant high doses.

Ascorbic acid
Subchronic and chronic studies in rats revealed no evidence of substance specific effects.

Mutagenic and tumourigenic potentials
Paracetamol
Extensive studies have revealed no evidence of a significant genotoxic risk associated with therapeutic, i.e. non-toxic, paracetamol doses. Long-term studies in rats and miceindicateno evidence of significant tumourigenic effects of non-hepatotoxic paracetamol dosages.

Chlorphenamine maleate
In vitro testings with chlorphenamine revealed no evidence of mutagenic potential relevant for clinical use.
Long-term studies in rats and mice revealed no evidence of a tumourigenic potential.

Caffeine
Like other methyl xanthines caffeine has a chromosome breaking potential *in vitro*. The total of scientific studies on metabolism and mutagenic properties of caffeine indicate that no mutagenic effects are to be expected *in vivo.* Long-term studies revealed no evidence of a carcinogenic potential of caffeine.

Ascorbic acid
Long-term mice studies no evidence of a tumourigenic potential was observed.
Cell culture or animal studies revealed no evidence of mutagenic potential within the therapeutical dosing range.

Reproduction toxicity
Paracetamol
Paracetamol crosses the placenta.
Animal studies and experience to date in humans have yielded no evidence of reproductive damages.

Chlorphenamine maleate

Chlorphenamine has been insufficiently tested for toxic risks on reproduction. There are no data concerning fertility and the effects on postnatal development.

Caffeine
Caffeine crosses the placenta. At very high caffeine doses conflicting results were seen in different animal species (rat, mouse, rabbit) concerning the fetal damaging effect. Embryotoxic and fetotoxic but no teratogenic effects were seen in rats after administration of very high caffeine doses (more than 100 mg per kg body weight). No increased risk for the course of pregnancy or the development of the child was observed at therapeutically significant doses of caffeine or the intake of coffee.

Ascorbic acid
Studies on two animal species with daily doses of 150, 250, 500 and 1000 mg per kg body weight revealed no evidence of foetotoxic effects. Ascorbic acid is excreted in breastmilk and crosses the placenta by simple diffusion.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Excipients: Gelatine, Glycerol tristearate, Lactose monohydrate.
Capsule shell: Capsule body – Gelatine, Water, Titanium dioxide (E 171); *Capsule cap:* Gelatine, Quinoline yellow (E 104), Water, Colorant Sunset yellow (E 110), Titanium dioxide (E 171)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
5 years.

6.4 Special precautions for storage
Do not store above 25°C.

6.5 Nature and contents of container
PVC/PVDC aluminium blister
Original package containing 10 capsules, hard.

6.6 Special precautions for disposal
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

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Stadastraße 2–18
61118 Bad Vilbel, Germany

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Fax: +496101 603259
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8. MARKETING AUTHORISATION NUMBER

6301368.00.00

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25. January 2005

10. DATE OF REVISION OF THE TEXT

May2014

11. LEGAL CATEGORY

Available only in pharmacies