SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Grippostad Day Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 300 mg paracetamol, 25 mg caffeine and 5 mg phenylephrine hydrochloride.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule, hard

Capsule with a white body and yellow cap.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Symptomatic relief of colds and influenza including fever, aches and pains, sore throat and nasal congestion.

4.2 Posology and method of administration

Recommended dose and dosage schedule

Adults (including older people)
2 capsules up to 4 times a day as required. Maximum dose should not exceed 8 capsules in 24 hours with at least 4 hours between doses.

Paediatric population
Children 12-18 years of age
2 capsules up to 3 times a day as required. Maximum dose should not exceed 6 capsules in 24 hours, with at least 4 hours between doses.

Children under 12 years of age

Grippostad Day Capsules should not be used in children under 12 years.

Method of administration
Oral use.

Grippostad Day Capsules should be used during daytime only, as it contains caffeine, which may cause insomnia (see section 4.8).

Duration of use
Grippostad Day Capsules should not be taken for more than 3 days without medical advice.

This product should not be administered for a longer period of time or in higher doses without consulting a physician (see section 4.4).

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- Glucose-6-phosphate dehydrogenase deficiency
- Phaeochromocytoma
- Hepatic disease
- Severe renal impairment
- Hypertension
- Hyperthyroidism
- Diabetes
- Heart disease
- Narrow angle glaucoma

Concomitant use with tricyclic antidepressants, or beta blocking drugs or MAO-inhibitors (within the last two weeks) see Section 4.5

4.4 Special warnings and precautions for use

Medical advice should be sought before using this product in patients with these conditions:

- An enlargement of the prostate gland
- Occlusive vascular disease (e.g. Raynaud's phenomenon)
- Cardiovascular disease

This product should not be used by patients taking other sympathomimetics (such as decongestants, appetite suppressants and amphetamine-like psychostimulants) (see Section 4.5).

Excessive intake of caffeine (e.g. coffee, tea and some canned drinks) should be avoided while taking this product.
Caution is advised in patients with chronic excessive alcohol intake.

An increase of the recommended paracetamol dose can lead to severe and potential fatal liver damage (see Section 4.9). To avoid the risk of overdosage, no other paracetamol-containing medicine should be used concomitantly.

Care is advised in the administration of paracetamol to patients with renal or hepatic impairment. The hazard of overdose is greater in those with non-cirrhotic alcoholic liver disease.

In case of high fever, signs of a secondary infection or duration of symptoms for more than

three days, medical consultation is recommended.

In general, paracetamol-containing medicinal products should not be used for more than a few days or in higher doses without medical advice.

4.5 Interaction with other medicinal products and other forms of interaction

Enzyme-inducing drugs may increase hepatic damage, as does excessive intake of alcohol. Substances shown to delay gastric emptying rate (like propantheline and narcotic analgesics pethidine, pentazocine, and certain foodstuffs, especially carbohydrates) consequently slow the rate of paracetamol absorption. Similarly, drugs which promote gastric emptying such as metoclopramide and domperidone may increase the rate of paracetamol absorption. Cholestyramine reduces the absorption of paracetamol.

These interactions are considered to be of unlikely clinical significance in acute usage at the dosage regimen proposed.

Medical advice should be sought before taking paracetamol-caffeine phenylephrine in combination with the following drugs:

- *Monoamine oxidase inhibitors (including moclobemide):* Hypertensive interactions occur between sympathomimetic amines such as phenylephrine and monoamine Oxidase inhibitors (see contraindications).
- *Sympathomimetic amines:* Concomitant use of phenylephrine with other sympathomimetics amines can increase the risk of cardiovascular side effects (see warnings and precautions).
- *Beta-blockers and other antihypertensives (including debrisoquine, guanethidine, reserpine, methyldopa):* Phenylephrine may reduce the efficacy of beta-blocking drugs and antihypertensive drugs. The risk of hypertension and other cardiovascular side effects may be increased (see contraindications).
- *Tricyclic antidepressants (eg amitriptyline):* May increase the risk of cardiovascular side effects with phenylephrine (see contraindications).
- *Digoxin and cardiac glycosides*: Concomitant use of phenylephrine with digoxin or cardiac glycosides may increase the risk of irregular heartbeat or heart attack.
- *Ergot alkaloids* (ergotamine and methysergide) increased risk of ergotism.

Warfarin and other coumarins: The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular daily use of paracetamol with an increased risk of bleeding; occasional doses have no significant effect.

4.6 Fertility, pregnancy and lactation

Pregnancy

This product is not recommended for use in pregnancy due to the phenylephrine and caffeine content.

There is a potential increased risk of lower birth weight and spontaneous abortion associated with caffeine consumption during pregnancy.

Breastfeeding

This product should not be used while breast-feeding without medical advice.

Caffeine in breast milk may have a stimulating effect on breast-fed infants.

Phenylephrine may be excreted in breast milk.

4.7 Effects on ability to drive and use machines

This product has minor or moderate influence on the patient's ability to drive or and use machines. Especially at the start of treatment, on increasing the dose or switching medication and in conjunction with alcohol.

4.8 Undesirable effects

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

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 (cannot be estimated from the available data).

Blood and lymphatic system disorders
Not known: Thrombocytopenia, leukopenia, agranulocytosis, pancytopenia.

Immune system disorders
Not known: Allergic reactions (angiooedema, dyspnoea, sweating, nausea, hypotension until shock), anaphylaxis. Cutaneous hypersensitivity reactions including skin rashes.

Nervous system disorders
Not known: Tiredness, headache, dizziness, insomnia, anxiety, nervousness, irritability, restlessness and excitability.

Eye disorders
Not known: Worsening of a pre-existing narrow-angle glaucoma Mydriasis, acute angle closure glaucoma, most likely to occur in those with closed angle glaucoma.

Cardiac disorders
Not known: Hypertension, palpitations, tachycardia.

Respiratory, thoracic and mediastinal disorders
Not known: Bronchospasm.

Gastrointestinal disorders
Not known: Dry mouth, nausea, vomiting, diarrhoea, anorexia.

Hepatobiliary disorders
Very rare: Hepatic dysfunction.

Skin and subcutaneous tissue disorders
Very rare: Very rare cases of serious skin reactions have been reported
Not known: Allergic reactions (e.g. rash, urticaria, allergic dermatitis). Hypersensitivity reactions – including that cross-sensitivity may occur with other sympathomimetics.

Renal and urinary disorders
Not known: Renal dysfunction, dysuria, urinary retention. This is most likely to occur in those with bladder outlet obstruction, such as prostatic hypertrophy.

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 Yellow Card Scheme. Website: www.mhra.gov.uk/yellowcard.

4.9 Overdose

Paracetamol

Liver damage is possible in adults who have taken 10g or more of paracetamol but has also occurred at doses lower than this. Ingestion of 5 g or more of paracetamol may lead to liver damage if the patient has risk factors (see below).

Risk factors:
If the patient
a: Is on long term treatment with carbamazepine, phenobarbitone, phenytoin, primidone,

rifampicin, St John's Wort or other drugs that induce liver enzymes.

Or
b: Regularly consumes ethanol in excess of recommended amounts.

Or
c: Is likely to be glutathione deplete e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia.

Symptoms
Symptoms of paracetamol overdosage in the first 24 hours are pallor, nausea, vomiting, anorexia and abdominal pain. Liver damage may become apparent 12 to 48 hours after ingestion. Abnormalities of glucose metabolism and metabolic acidosis may occur. In severe poisoning, hepatic failure may progress to encephalopathy, haemorrhage, hypoglycaemia, cerebral oedema, and death. Acute renal failure with acute tubular necrosis, strongly suggested by loin pain, haematuria and proteinuria, may develop even in the absence of severe liver damage. Cardiac arrhythmias and pancreatitis have been reported.

Treatment
Immediate treatment is essential in the management of paracetamol overdose. Despite a lack of significant early symptoms, patients should be referred to hospital urgently for immediate medical attention. Symptoms may be limited to nausea or vomiting and may not reflect the severity of overdose or the risk of organ damage. Management should be in accordance with established treatment guidelines, see BNF overdose section.

Treatment with activated charcoal should be considered if the overdose has been taken within 1 hour. Plasma paracetamol concentration should be measured at 4 hours or later after ingestion (earlier concentrations are unreliable). Treatment with N-acetylcysteine may be used up to 24 hours after ingestion of paracetamol, however, the maximum protective effect is obtained up to 8 hours postingestion. The effectiveness of the antidote declines sharply after this time. If required the patient should be given intravenous N-acetylcysteine, in line with the established dosage schedule. If vomiting is not a problem, oral methionine may be a suitable alternative for remote areas, outside hospital. Management
of patients who present with serious hepatic dysfunction beyond 24 h from ingestion should be discussed with the NPIS or a liver unit.

Caffeine
Symptoms
Overdose of caffeine may result in epigastric pain, vomiting, diuresis, tachycardia or cardiac arrhythmia, CNS stimulation (insomnia, restlessness, excitement, agitation, jitteriness, tremors and convulsions).
It must be noted that for clinically significant symptoms of caffeine overdose to occur with this product, the amount ingested would be associated with serious paracetamol-related liver toxicity.

Treatment
No specific antidote is available, but supportive measures may be used.

Phenylephrine
Symptoms
Phenylephrine overdosage is likely to result in effects similar to those listed under adverse reactions. Additional symptoms may include hypertension, and possibly reflex bradycardia. In severe cases confusion, hallucinations, seizures and arrhythmias may occur. However the amount required to produce serious phenylephrine toxicity would be greater than that required to cause paracetamol-related liver toxicity.

Treatment

Treatment should be as clinically appropriate. Severe hypertension may need to be treated with alpha blocking drugs such as phentolamine.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other cold combination preparations, paracetamol combinations
ATC code: R05XA01

Paracetamol

Analgesic effect: Paracetamol is most effective in relieving low intensity pain of nonvisceral origin. Paracetamol does not have antiinflammatory effects.

Antipyretic effect: Paracetamol produces antipyresis by a mechanism similar to that of salicylates. Paracetamol lowers body temperature in patients with fever but rarely lowers normal body temperature. The drug acts on the hypothalamus to produce antipyresis; heat dissipation is increased as a result of vasodilatation and increased peripheral blood flow. Paracetamol reduces fever by inhibiting the action of endogenous pyrogen on hypothalamic heat-regulating centres.

Phenylephrine

Phenylephrine is an α-adrenoceptor stimulant with little effect on ß-adrenoceptors of the heart. Adrenergic nasal decongestants act by stimulating α-adrenoceptors of vascular smooth muscle, thus constricting dilated arterioles within nasal mucosa and reducing blood flow in engorged, oedematous area. Eustachian tube function is also improved.

Caffeine

Caffeine potentiates the therapeutic potential of paracetamol. A slightly positive influence of caffeine on the absorption rate of paracetamol was seen: caffeine increased the AUC and the Cmax of paracetamol by 29% and 15%, respectively.

5.2 Pharmacokinetic properties

Absorption

Paracetamol: Paracetamol is rapidly absorbed from the gastrointestinal tract, reaching peak plasma levels within 40 to 60 min. The oral administration shows an absolute bioavailability of 60-70%. The area under the concentration versus time curve increases proportionally with dose, indicating linearity of pharmacokinetics.

Phenylephrine: Phenylephrine is absorbed after oral administration, however, its bioavailability is only 38% due to first-pass metabolism. Concentrations of phenylephrine increase linearly with an increase in dosage. The accumulation index is 1.6 for phenylephrine following repeated dosing.

Caffeine: Caffeine is readily absorbed after oral administration. Maximal plasma concentrations of caffeine are achieved within 1 h. With increasing doses AUC increases disproportionately indicating non-linear kinetics. Caffeine exhibits dose-dependent pharmacokinetics.

Distribution and Protein binding

Paracetamol: Paracetamol is rapidly and uniformly distributed into most body tissues. About 25% of paracetamol in blood is bound to plasma proteins. Volume of distribution is in the order of magnitude of 1 l/kg in various species. Paracetamol is transferred across the placenta with an extraction ratio of 0.12. Paracetamol passes rapidly into milk of nursing mothers.

Phenylephrine: The volume of distribution during steady state, however (184-543 l), considerably exceeded body weight, indicating storage in various compartments. No data exist on the extent of protein binding. Penetration into the brain appears to be minimal, and the drug does not seem to be excreted to any great extent in breast milk.

Caffeine: Caffeine Methylxanthines are distributed into all body compartments; they cross the placenta and pass into breast milk. The apparent volume of distribution is 0.4 -0.6 l/kg. At therapeutic concentrations, the protein binding of theophylline averages about 60%.

Metabolism and Elimination

Paracetamol: Paracetamol is almost completely cleared from the body by biotransformation. Paracetamol is metabolised by microsomal enzyme systems in the liver. About 80-85% of the paracetamol in the body undergoes conjugation principally with glucuronic acid and to a lesser extent with sulphuric acid. A small amount of paracetamol is also conjugated with cysteine. A small amount of paracetamol is also deacetylated. When there is a deficiency in glutathione, the hepatotoxic metabolite N-acetyl-p-benzoquinoneimine is generated. Paracetamol is excreted in urine principally as paracetamol glucuronide with small amounts of paracetamol sulphate and mercaptate and unchanged drug. Approximately 85% of a dose of paracetamol is excreted in urine as free and conjugated paracetamol. Paracetamol has a plasma half-life of 1.25-3 h.

Phenylephrine: Phenylephrine undergoes extensive biotransformation in the intestinal wall and in the liver, which accounts for the bioavailability of only 38% after oral administration. The principal routes of metabolism are to sulphate conjugates, which are formed largely in the gut wall, and oxidative deamination by monoamine oxidase. Some glucuronidation of phenylephrine also occurs. Both unchanged phenylephrine and its metabolites are excreted almost entirely in the urine. Only a small amount of the drug is excreted unchanged, 2.6 % after oral administration. The elimination half-life of phenylephrine varies between 2.1 and 3.4 h.

Caffeine: Caffeine Methylxanthines are eliminated primarily by metabolism in the liver. Only 5% of administered caffeine are recovered unchanged in the urine. Caffeine is metabolised in man by demethylation to 1-and 7-methylxanthine, 1,7-dimethylxanthine and 1,3-dimethyluric acid and by oxidation at position 8. The major pathway in man proceeds through the formation of paraxanthine (1,7-dimethylxanthine), leading to the principal urinary metabolite, 1-methylxanthine, 1-methyluric acid, and an acetylated uracil derivative. At least four human CYP isoforms are involved in caffeine metabolism. The percentage of caffeine excreted unchanged in the urine is low, 1.2 - 3.0 %. Elimination half-life is in the range of 1 to 4 h in various species.

Kinetics in patients with impaired renal/hepatic function

Paracetamol: Impaired elimination of paracetamol was found in hepatitis patients, while peak plasma concentrations were unaffected. The sulphate and glucuronide metabolites of paracetamol accumulated substantially in patients with renal failure.

Phenylephrine: No data are available on the kinetics in renal failure. However, since only 16% of an oral dose of phenylephrine is excreted unchanged in urine within 24 h a decrease in renal function is likely to decrease its clearance significantly, thus prolonging the half-life and resulting in accumulation with related adverse effects. Since phenylephrine is metabolised to a greater extent of an oral dose in the gut wall and a lower fraction in the liver hepatic insufficiency is unlikely to result in major changes with oral administration.

Caffeine: Caffeine disposition is not significantly altered by liver cirrhosis.

Kinetics in elderly people

Paracetamol: Plasma paracetamol concentration was unaffected by age. The sulphate and glucuronide metabolites of paracetamol accumulated to a low degree in elderly controls. Elimination half-life averaged 2.7 h and was not related to age or sex. Volume of distribution declined with age in both sexes. Paracetamol clearance tended to decline with age in both sexes, but differences were of borderline significance.

Phenylephrine: Minimal data are available on the kinetics of phenylephrine in the elderly. In one study the observed half-life of 8.1 h was about 45% longer in the elderly, and the apparent volume of distribution was about 25% higher. Even though children use oral decongestants extensively, no pharmacokinetic data in the paediatric population are available. Renal elimination may, however, be compromised in the very young child.

Caffeine: Comparing the pharmacokinetics of caffeine in healthy young and elderly men time to peak concentration, peak concentration, and the percentage of the peroral dose systemically available were essentially identical in both age groups. Elimination half- lives ranged from 2.27 - 9.87 h. The average volume of distribution was significantly lower in the elderly subjects.

The **combination treatment of paracetamol, caffeine and phenylephrine** is supported by both the comparable pharmacokinetic features of the drugs and by the increased pharmacodynamic efficacy of the combination which complement each other. The interaction potential of the combination appears to be low. There is no evidence available that would support an increased toxicological hazard of the combination in addition to the effects of the single drugs except an increased pharmacodynamic response.

5.3 Preclinical safety data

Pre-clinical safety data on these active ingredients in the literature have not revealed any pertinent and conclusive findings which are of relevance to the recommended dosage and use of the product and which have not already been mentioned elsewhere in this Summary of Product Characteristics.

The toxicity of paracetamol has been extensively studied in numerous animal species. Pre-clinical studies in rats and mice have indicated single dose oral LD50 values of 3.7 g/kg and 338 mg/kg, respectively. Chronic toxicity in these species at large multiples of the human therapeutic dose occurs as degeneration and necrosis of hepatic, renal and lymphoid tissue, and blood count changes. The metabolites believed responsible for these effects have also been demonstrated in man. Paracetamol should not, therefore, be taken for long periods of time, and in excessive doses. At normal therapeutic doses, paracetamol is not associated with

genotoxic or carcinogenic risk. There is no evidence of embryo-or foetus-toxicity from paracetamol in animal studies.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium laurylsulphate
Silica colloidal anhydrous
Magnesium stearate

Capsules shell:
Gelatin
Titanium dioxide (E 171)
Yellow iron oxide (E 172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

30 months

6.4 Special precautions for storage

Do not store above 25°C
Store in the original package.

6.5 Nature and contents of container

Aluminium (Alu/Alu) blister strips, sealed with aluminium foil

Blister strips are packed into cardboard cartons.

Pack sizes are 10, 12, 20 and 24 capsules.

Not all pack sizes are marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

STADA Arzneimittel AG

Stadastrasse 2-18

61118 Bad Vilbel

Germany

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PL 11204/0265

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