SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Wockhardt Max Strength Cold & Flu Capsules
Health Essentials Max Strength Cold & Flu Relief Capsules
Numark Max Strength Cold & Flu with decongestant Capsules
Numark Max Strength Sinus relief with decongestant Capsules
Well Pharmaceuticals Max Strength Cold & Flu Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Paracetamol	500mg
Caffeine	25mg
Phenylephrine hydrochloride	6mg

Excipient(s) with known effect
For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Capsules

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the relief of nasal congestion and congestion of mucous membranes of the upper respiratory tract associated with the common cold, and relief of cold and influenza, including relief of aches and pains, sore throat, headache, fatigue and drowsiness, and lowering of temperature.

4.2 Posology and method of administration

Posology

Adults and children 16 years and over: 1-2 capsules every 4-6 hours. Maximum of 8 capsules in any 24 hour period.

Children 12 – 15 years: One capsule. Every 4-6 hours when necessary to maximum of 4 doses in 24 hours.

Children under 12 years of age: Do not give to children under 12 years.

Do not take for more than 3 days without consulting a doctor.

Method of administration

For oral administration. Swallow whole with water. Do not chew.

4.3 Contraindications

Hypersensitivity to paracetamol, caffeine, phenylephrine or to any of the excipients listed in section 6.1.

Caffeine:

Do not give to patients with a history of peptic ulceration.

Phenylephrine hydrochloride

- Hyper susceptible patients
- Hyperthyroidism
- Aneurysm
- Arteriosclerosis
- Phaeochromocytoma
- Cardiovascular disease including Hypertension
- Prostatic enlargement
- Diabetes mellitus
- Closed angle glaucoma
- Concomitant use with other sympathomimetic decongestants
- Beta-blockers – (see section 4.5)
- Monoamine oxidase inhibitors (MAOIs), including moclobemide (or within the last two weeks)
- Tricyclc antidepressants

4.4 Special warnings and precautions for use

Paracetamol

Care is advised in the administration of paracetamol to patients with renal or hepatic impairment. The hazards of overdose are greater in those with alcoholic liver disease. Paracetamol should be given with care to patients with alcoholic dependence.
Paracetamol is well tolerated by the majority of people with asthma. However, a small percentage of aspirin sensitive asthmatics are also sensitive to paracetamol. The likelihood of a reaction to paracetamol increases with a patient's level of sensitivity to aspirin (see section 4.8 Undesirable Effects).

Caution should be exercised when using paracetamol prior to (less than 72 hours) or concurrently with intravenous busulfan.

Cases of high anion gap metabolic acidosis (HAGMA) due to pyroglutamic acidosis have been reported in patients with severe illness such as severe renal

impairment and sepsis, or in patients with malnutrition or other sources of glutathione deficiency (e.g. chronic alcoholism) who were treated with paracetamol at therapeutic dose for a prolonged period or a combination of paracetamol and flucloxacillin. If HAGMA due to pyroglutamic acidosis is suspected, prompt discontinuation of paracetamol and close monitoring is recommended. The measurement of urinary 5-oxoproline may be useful to identify pyroglutamic acidosis as underlying cause of HAGMA in patients with multiple risk factors.

Caffeine

Care is advised in the administration of caffeine to patients with cardiac disease.

Excessive intake of caffeine (e.g. coffee, tea and some canned drinks) should be avoided while taking this product.

Phenylephrine

- Care is advised in the administration of phenylephrine in patients with cardiovascular conditions such as hypertension, occlusive vascular disease, Prinzmetal's angina, thromboembolic disorders, following myocardial infarction or a history of ischaemic heart disease.
- Phenylephrine should be used with caution in elderly patients.

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

If any of the following occur, this product should be stopped.

- Hallucinations
- Restlessness
- Sleep disturbances

The following warnings appear in the leaflet and on the label:

Label-
Contains paracetamol.
Do not take more medicine than the label tells you to. If you do not get better, talk to your doctor.
Do not take anything else containing paracetamol while taking this medicine.
Talk to a doctor at once if you take too much of this medicine, even if you feel well.

Leaflet-
Talk to a doctor at once if you take too much of this medicine even if you feel well. This is because too much paracetamol can cause delayed, serious liver damage.

General points:

- Do not exceed the recommended dose.
- If symptoms persist consult a doctor.
- Do not give to children under 12 years.
- Keep out of the reach and sight of children.
- Do not take for more than three days unless your doctor agrees.

Patients should be advised not to take other paracetamol-containing products concurrently.

4.5 Interaction with other medicinal products and other forms of interaction

Paracetamol

Alcohol:	Paracetamol should be given with care to patients with alcohol dependence (see Section 4.4).
Analgesics	Diflunisal increases blood concentrations of paracetamol.
Anion–exchange resins:	Absorption reduced by colestyramine; administration should be separated by at least 1 hour.
Antibacterials	Isoniazid may increase the risk of hepatotoxicity with therapeutic doses of paracetamol. Caution should be taken when paracetamol is used concomitantly with flucloxacillin as concurrent intake has been associated with high anion gap metabolic acidosis due to pyroglutamic acidosis, especially in patients with risks factors (see section 4.4).
Anticoagulants	The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular use of paracetamol with increased risk of bleeding; occasional doses have no significant effect.
Antiepileptics	Carbamazepine, phenobarbital, phenytoin and primidone can reduce the effects of paracetamol and increase the risk of hepatotoxicity. Paracetamol may increase lamotrigine metabolism.
Motility stimulants	The speed of absorption of

	paracetamol may be increased by metoclopramide or domperidone.
Oral Contraceptives	Paracetamol is cleared from the body more quickly in women taking oral contraceptives and the analgesic effects may be reduced.
Uricosurics	Probenecid can reduce the loss of paracetamol from the body.

Caffeine

Antibacterials:	Some quinolone antibiotics, including enoxacin, pipemidic acid and ciprofloxacin can reduce the clearance of caffeine and prolong its plasma half-life.
Antidepressants	Fluvoxamine can reduce the clearance of caffeine and increase its stimulant and side effects.
Antiepileptics	Phenytoin may increase the clearance of caffeine.
Benzodiazepines	Caffeine can reduce the sedative effects of diazepam.
Disulfiram	May reduce the clearance of caffeine.
Lithium	Caffeine may increase the clearance of lithium.
Mexiletine	May reduce the clearance of caffeine.
Oestrogens and progestogens	Oral contraceptives or oestrogen replacement therapy may reduce the clearance of caffeine.
Phenylpropanolamine	Concomitant administration may increase blood pressure, resulting in hypertensive crises in a few susceptible individuals. Manic psychosis has occurred. Phenylpropanolamine can increase serum caffeine levels.
Theophylline	Concomitant administration can increase plasma theophylline and plasma caffeine levels.

Phenylephrine Hydrochloride

Phenylephrine should be used with caution in combination with the following drugs as interactions have been reported.

Adrenergic neurone blockers	May enhance the hypertensive effect of

	phenylephrine.
Atropine	There is an increased risk of hypertension when used with atropine.
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.
Digoxin and cardiac glycosides	Increase the risk of irregular heartbeat or heart attack
Ergot alkaloids	E.g. (ergotamine and methylsergide) increased risk of ergotism.
Monoamine oxidase inhibitors (including moclobemide)	Hypertensive interactions occur between sympathomimetic amines such as phenylephrine and monoamine oxidase inhibitors (see contraindications).
Oxytocin	Potential increased risk of hypertension with oxytocin.
Sympathomimetic amines	Concomitant use of phenylephrine with other sympathomimetic amines can increase the risk of cardiovascular side effects (hypertensive effects).
Tricyclic antidepressants (e.g. amitriptyline)	There is an increased risk of hypertension when used with tricyclic antidepressants e.g. imipramine.

4.6 Fertility, pregnancy and lactation

Paracetamol

Epidemiological studies in human pregnancy have shown no ill effects due to paracetamol used in the recommended dosage, but patients should follow the advice of their doctor regarding its use. A large amount of data on pregnant women indicate neither malformative, nor feto/neonatal toxicity. Epidemiological studies on neurodevelopment in children exposed to paracetamol in utero show inconclusive results. If clinically needed, paracetamol can be used during pregnancy however it should be used at the lowest effective dose for the shortest possible time and at the lowest possible frequency.

Paracetamol is excreted in breast milk but not in a clinically significant amount. Available published data do not contraindicate breast-feeding.

Caffeine

Taken during pregnancy, it appears that the half-life of caffeine is prolonged. This is a possible contributing factor in hypermesis gravidarum. Caffeine crosses the placenta, and foetal blood and tissue levels similar to maternal

concentrations are achieved. Cardiac dysrhythmias have been noted in the foetuses and neonates of mothers consuming varying levels of caffeine during pregnancy. Decreased birth weight may be associated with maternal caffeine intake and cigarette smoking. Limited evidence suggests that high maternal caffeine intake may be associated with fetotoxicity including spontaneous abortion, however, other factors may have contributed to the findings. Decreased fertility may be associated with maternal caffeine intake. Caffeine intake during pregnancy should be kept to a minimum.

Caffeine is excreted in breast milk, but with moderate intake amounts are probably too low to be clinically significant. Regular intake of large amounts of caffeine by nursing mothers can affect the infant~~.~~**,** including irritability and poor sleeping patterns.

Phenylephrine hydrochloride:

The safety of phenylephrine during pregnancy has not been established but there is some evidence suggesting a possible association of foetal abnormalities with first trimester exposure to phenylephrine. As an alpha-adrenoceptor stimulant, phenylephrine might provoke uterine changes, which can result in foetal asphyxia and/or foetal bradycardia. There is no information on the excretion of phenylephrine into breast milk; however no clinical problems have been documented.

In view of the above, this product should be avoided during pregnancy and lactation unless prescribed by a doctor.

4.7 Effects on ability to drive and use machines

Paracetamol:

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

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

Phenylephrine Hydrochloride:
May cause dizziness, if affected, do not drive or operate machinery.

4.8 Undesirable effects

a) Summary of the safety profile

Adverse events of paracetamol from historical clinical trial data are both infrequent and from small patient exposure. Accordingly, events reported from extensive post-marketing experience at therapeutic/labelled dose and considered attributable are tabulated below by system class. The frequency of these adverse events is not known (cannot be estimated from available data).

Paracetamol:

Body System	**Adverse effect**
Blood and lymphatic system disorders	Thrombocytopenia Agranulocytosis These are not necessarily causally related to paracetamol.
Immune system disorders	Anaphylaxis Cutaneous hypersensitivity reactions including skin rashes, angiodema and Stevens Johnson syndrome, toxic epidermal necrolysis. A small percentage of aspirin-sensitive asthmatics are also sensitive to paracetamol. In such cases, the deterioration in respiratory function induced by paracetamol is milder and shorter than with aspirin (see section 4.4).
Metabolism and nutrition disorders	High anion gap metabolic acidosis
Respiratory, thoracic and mediastinal disorders	Bronchospasm*
Hepatobiliary disorders	Hepatic dysfunction
Renal and urinary disorders	Nephropathy has been associated with chronic high dose use.

* There have been cases of bronchospasm with paracetamol, but these are more likely in asthmatics sensitive to aspirin or other NSAIDs.

Caffeine:

Adverse reactions identified through post-marketing use with caffeine are listed below. The frequency of these reactions is unknown.

Central Nervous system	Nervousness and anxiety Irritability, Restlessness and Excitability Dizziness

When the recommended paracetamol-caffeine dosing regimen is combined with dietary caffeine intake, the resulting higher dose of caffeine may increase

the potential for caffeine-related adverse effects such as insomnia, restlessness, anxiety, irritability, headaches, gastrointestinal disturbances and palpitations.

Phenylephrine Hydrochloride:

The following adverse events have been observed in clinical trials and post-marketing reports with phenylephrine and may therefore represent the most commonly occurring adverse events.

Body System	**Undesirable effect**
Psychiatric disorders	Nervousness
Nervous system disorders	Headache, dizziness, insomnia
Cardiac disorders	Increased blood pressure
Gastrointestinal disorders	Nausea, vomiting, diarrhoea

Adverse reactions identified during post-marketing use are listed below. The frequency of these reactions is unknown.

Eye disorders	Mydriasis, acute angle closure glaucoma, most likely to occur in those with closed angle glaucoma
Cardiac disorders	Tachycardia, palpitations
Skin and subcutaneous disorders	Allergic reactions (e.g. rash, urticaria, allergic dermatitis). Hypersensitivity reactions – including that cross-sensitivity may occur with other sympathomimetics
Renal and urinary disorders	Dysuria, urinary retention. This is most likely to occur in those with bladder outlet obstruction, such as prostatic hypertrophy.

Description of selected adverse reactions

High anion gap metabolic acidosis

Cases of high anion gap metabolic acidosis due to pyroglutamic acidosis have been observed in patients with risk factors using paracetamol (see section 4.4). Pyroglutamic acidosis may occur as a consequence of low glutathione levels in these patients.

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 at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Paracetamol

Liver damage is possible in adults who have taken 10g or more of paracetamol. Ingestion of 5g 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, phenobarbital, 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 overdose in the first 24 hours are sweating, 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, hypotension, cerebral oedema, coma and death. Prothrombin time may increase with deteriorating liver function. 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 arrythmias 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 eight hours post ingestion. 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 hours from ingestion should be discussed with the NPIS or a liver unit.

Caffeine
Symptoms: Large doses may cause restlessness, excitement, psychosis, muscle tremor, tinnitus, hyperglycaemia, hypokalaemia, diuresis, dehydration, tachycardia and extrasystoles. Emesis and convulsions may occur.

Treatment
No specific antidote. Elimination may be enhanced by repeated oral doses of activated charcoal. Symptomatic and supportive treatment.

Hypokalemia should be corrected by intravenous infusion of potassium chloride.

Intravenous diazepam or barbiturates may be used to control convulsions.

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

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Paracetamol
Paracetamol has analgesic and antipyretic properties. Analgesic effects are thought to be related to inhibition of prostaglandin synthesis. An antipyretic effect has been demonstrated where fever exists but normal body temperature is not lowered. The drug acts on the hypothalamus to produce antipyresis; heat dissipation is increased as a result of vasodilation and increased peripheral blood flow. The failure of paracetamol to exert anti-inflammatory activity may be attributed to the fact that it is only a weak inhibitor of cyclo-oxygenase in the presence of the high concentrations of peroxides that are found in

inflammatory lesions. Further, paracetamol does not inhibit neutrophil activation, as do other NSAIDs.

Single or repeated therapeutic doses of paracetamol have no effect on the cardiovascular and respiratory systems, nor does the drug produce gastric irritation, erosion, or bleeding.

Caffeine

The primary effect of caffeine is central nervous system stimulation, mainly on the higher centres. This expressed in terms of increased vigilance, wakefulness, relief from fatigue, increased mental activity, improved performance and improved mood. Other effects include diuresis and increased cardiac output with peripheral vasodilation. Caffeine, a methylxanthine, exerts its pharmacological effects by increasing calcium permeability in the sarcoplasmic reticulum, inhibiting phosphodiesterase and promoting accumulation of cyclic AMP. Caffeine is also a competitive, non-selective antagonist at adenosine A_1 and A_{2A} receptors. Evidence suggests that adenosine receptor antagonism is the most important factor responsible for most pharmacological effects of methylxanthines in doses that are administered therapeutically.

Phenylephrine

Phenylephrine is a relatively selective α_1-adrenoceptor agonist. It has weak α_2-adrenoceptor agonist activity, some activity as a low cardioselective β-adrenoceptor agonist and minimal central stimulant activity. It is also termed a sympathomimetic vasoconstrictor. Most of the α_1-stimulant activity is due to an indirect effect via release of noradrenaline. Sympathomimetic vasoconstriction forms the basis of its decongestant actions, for which it is most widely used.

5.2 Pharmacokinetic properties

Paracetamol:

Paracetamol is rapidly and almost completely absorbed from the gastrointestinal tract, with peak plasma concentrations reached in 10-15 minutes after oral dosing. Dissolution and gastric emptying are rate-limiting steps; the mean half-time of absorption from upper small intestine is within minutes. The absolute oral bioavailability is about 80% and is independent of dose in the range 5 to 20 mg/kg. Oral bioavailability of paracetamol is subject to first pass metabolism. Paracetamol is rapidly and uniformly distributed into most body tissues. About 25% of paracetamol in blood is bound to plasma proteins. The mean plasma paracetamol half-life following a therapeutic dose is about 2.3 hours in healthy adults, with a range of 1.5-3 hours. Paracetamol crosses the placenta and is present in breast milk.

After therapeutic doses, 90 - 100% of the drug may be recovered in the urine within the first day, primarily after hepatic conjugation with glucuronic acid (about 60%), sulfuric acid (about 35%) or cysteine (about 3%); small amounts of hydroxylated and deacetylated metabolites have also been detected. A small proportion of paracetamol undergoes P450-mediated N-hydroxylation to form

N-acetyl-benzoquinoneimine, a highly reactive intermediate. After large doses of paracetamol, this metabolite is formed in amounts sufficient to deplete hepatic glutathione. Under these circumstances, reaction with sulfhydryl groups in hepatic proteins is increased and hepatic necrosis can result. Renal clearance is about 10 ml/min.

Caffeine:
Caffeine is absorbed readily after oral administration to the extent of 99%, peak plasma levels occur in 15-45 min. The half-life of caffeine in plasma shows considerable variation with the reported values ranging from 3.0-7.5 hours. It is widely and rapidly distributed throughout the body, and passes readily into the central nervous system and saliva. Approximately 17% of the drug is bound to plasma proteins. Caffeine crosses the placenta and has been shown to distribute into milk in a milk-to-serum concentration of 0.52.

In adults, caffeine is metabolised almost completely in the liver via oxidation, demethylation, and acetylation, and is excreted in the urine as 1-methyluric acid, 1-methylxanthine and other metabolites with only about 1% unchanged. Neonates have a greatly reduced capacity to metabolise caffeine and it is largely excreted unchanged in the urine until hepatic metabolism becomes significantly developed.

Phenylephrine
Phenylephrine is absorbed after oral administration but is subject to extensive presystemic metabolism, much of which occurs in the enterocytes. As a consequence, systemic bioavailability is only about 40%. Following administration, peak plasma concentrations are achieved in 1-2 h. The mean plasma half-life is in the range 2-3 h. Penetration into the brain appears to be minimal.

Phenylephrine undergoes extensive biotransformation in the liver. Both phenylephrine and its metabolites are excreted in urine, with less than 20% as unchanged drug. The principal routes of metabolism are to sulfate conjugates, formed largely in the gut wall, and deamination by monoamine oxidase. There are no data on the extent of protein binding. Excretion in breast milk appears to be minimal.

5.3 Preclinical safety data

The active ingredients have been in widespread use for many years and have a well-established therapeutic profile. There is no further data of relevance to the prescriber in addition to that presented in the other sections of the SmPC. Conventional studies using the currently accepted standards for the evaluation of toxicity to reproduction and development are not available.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Pregelatinised starch
Sodium lauryl sulfate
Croscarmellose sodium
Magnesium stearate
Talc
Purified water
Empty hard gelatin capsule shell (E-171, E-127, E-104 and E-131)

6.2 Incompatibilities

None

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 25ºC

6.5 Nature and contents of container

Capsules are packaged in blister strips

Blister strips consist of a 35gsm paper/9µ soft tempered aluminium foil lid and 250µ PVDC film base in cartons.

Pack sizes: 12, 16 (GSL)

6.6 Special precautions for disposal

No special requirements for disposal

7 MARKETING AUTHORISATION HOLDER

Wockhardt UK Ltd
Ash Road North
Wrexham
LL13 9UF
UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 29831/0172

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21/06/2003
Date of latest renewal: 23/02/2011

10 DATE OF REVISION OF THE TEXT

02/05/2025