SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Care Max Strength Cold & Flu Relief 400mg/10mg Film-Coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains active substances:
400.0 mg Ibuprofen
10.0 mg Phenylephrine hydrochloride

Excipient with known effect
Each tablet contains up to 2.92 mg sodium

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Care Max Strength Cold & Flu Relief Tablets are white, oval, biconvex film coated tablets (tablets) with a breaking notch on one side and 10 mm diameter. The breaking notch is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Symptomatic treatment of mild to moderate pain or fever and nasal congestion related to colds and influenza in adults and adolescents older than 12 years of age.

4.2 Posology and method of administration

Posology

For short-term use only.

One tablet every 8 hours. Leave at least 4 hours between doses and do not exceed three tablets in any 24 hour period.

Adults, the elderly and adolescents over 12 years

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to relieve symptoms (see section 4.4). The patient should consult a doctor if symptoms persist or worsen, or if the medicinal product is required for more than 10 days.

Children

Not to be given to children under 12 years.

Method of administration

For oral use

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- Hypertension and severe coronary heart disease.
- Patients who have previously shown hypersensitivity reactions (e.g. asthma, rhinitis, angioedema or urticaria) in response to acetylsalicylic acid or other non-steroidal anti-inflammatory drugs (NSAIDs).
- Active or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes or proven ulceration or bleeding).
- History of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy.
- Severe heart failure (NYHA Class IV), renal failure or hepatic failure (see section 4.4).
- Last trimester of pregnancy.
- Use with concomitant NSAIDs including cyclo-oxygenase-2 specific inhibitors (see section 4.5).
- Hyperthyroidism.
- Contraindicated in patients currently receiving or within two weeks of stopping therapy with monoamine oxidase inhibitors.

4.4 Special warnings and precautions for use

Ibuprofen

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see gastrointestinal and cardiovascular risks below).

Elderly

The elderly are at increased risk of consequence of adverse reactions to NSAIDs, especially gastrointestinal bleeding and perforation which may be fatal.

Respiratory

Bronchospasm may be precipitated in patients suffering from or with a previous history of bronchial asthma or allergic disease.

Other NSAIDs

The use of this medicinal product with concomitant NSAIDs, including cyclo-oxygenase-2 selective inhibitors, should be avoided (see section 4.5).

SLE and mixed connective tissue disease

Systemic lupus erythematosus and mixed connective tissue disease - increased risk of aseptic meningitis (see section 4.8).

Renal

Renal impairment as renal function may further deteriorate (see sections 4.3 and 4.8).

Hepatic

Hepatic dysfunction (see sections 4.3 and 4.8).

Cardiovascular and cerebrovascular effects

Caution (discussion with doctor or pharmacist) is required prior to starting treatment in patients with a history of hypertension and/or heart failure as fluid retention, hypertension and oedema have been reported in association with NSAID therapy.

Clinical studies suggest that use of ibuprofen, particularly at a high dose (2,400 mg/day) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke). Overall, epidemiological studies do not suggest that low dose ibuprofen (e.g. ≤ 1,200 mg/day) is associated with an increased risk of arterial thrombotic events.

Patients with uncontrolled hypertension, congestive heart failure (NYHA II-III), established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with ibuprofen after careful consideration and high doses (2,400 mg/day) should be avoided.

Careful consideration should also be exercised before initiating long-term treatment of patients with risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking), particularly if high doses of ibuprofen (2,400 mg/day) are required.

Impaired female fertility

There is limited evidence that drugs which inhibit cyclo-oxygenase/prostaglandin synthesis may cause impairment of female fertility by an effect on ovulation. This is reversible on withdrawal of treatment.

Gastrointestinal

NSAIDs should be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) as these conditions may be exacerbated (see section 4.8).

GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at any time during treatment, with or without warning symptoms or a previous history of serious GI events.

The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (see section 4.3), and in the elderly. These patients should commence treatment on the lowest dose available.

Patients with a history of GI toxicity, particularly the elderly, should report any unusual abdominal symptoms (especially GI bleeding), particularly in the initial stages of treatment.

Caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors or anti-platelets agents such as acetylsalicylic acid (see section 4.5).

When GI bleeding or ulceration occurs in patients receiving ibuprofen, the treatment should be withdrawn.

Severe skin reactions Dermatological

Serious skin reactions, some of them fatal, including exfoliating dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported rarely in association with the use of NSAIDs (see section 4.8). Patients appear to be at highest risk of these reactions early in the course of therapy, the onset of the reaction occurring in the majority of cases within the first month of treatment. Acute generalised exanthematous pustulosis (AGEP) has been reported in relation to ibuprofen-containing products. This medicinal product should be discontinued at the first appearance of skin rash, mucosal lesions or any other sign of hypersensitivity.

Masking of symptoms of underlying infections

This product can mask symptoms of infection, which may lead to delayed initiation of appropriate treatment and thereby worsening the outcome of the infection. This has been observed in bacterial community acquired pneumonia and bacterial complications to varicella. When this product is administered for fever or pain relief in relation to infection, monitoring of infection is advised. In nonhospital settings, the patient should consult a doctor if symptoms persist or worsen.

Phenylephrine

Phenylephrine should be used with care in patients with cardiovascular disease, diabetes mellitus, closed angle glaucoma, prostatic enlargement and hypertension.

Paediatric population

There is a risk of renal impairment in dehydrated adolescents.

This medicine contains sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

The product is contraindicated in combination with:

Monoamine Oxidase Inhibitors (MAOIs)

Hypertensive interactions occur between sympathomimetic amines such as phenylephrine hydrochloride and monoamine oxidase inhibitors (see section 4.3).

The product should be avoided in combination with:

Acetylsalicylic acid

Concomitant administration of ibuprofen and acetylsalicylic acid is not generally recommended because of the potential of increased adverse effects unless low-dose acetylsalicylic acid (not above 75 mg daily) has been advised by a doctor (see section 4.4).

Experimental data suggest that ibuprofen may competitively inhibit the effect of low dose acetylsalicylic acid on platelet aggregation when they are dosed concomitantly. Although there are uncertainties regarding extrapolation of these data to the clinical situation, the possibility that regular, long-term use of ibuprofen may reduce the cardioprotective effect of low-dose acetylsalicylic acid cannot be excluded. No clinically relevant effect is considered to be likely for occasional ibuprofen use (see section 5.1).

Other NSAIDs including cyclo-oxygenase-2 selective inhibitors

Avoid concomitant use of two or more NSAIDs as this may increase the risk of adverse reactions (see section 4.4).

The product should be used with caution in combination with:

Anti-coagulants

NSAIDs may enhance the effects of anticoagulants such as warfarin (see section 4.4).

Antihypertensives (ACE inhibitors and Angiotensin II Antagonists) and diuretics

NSAIDs may diminish the effect of these drugs. In some patients with compromised renal function (e.g. dehydrated patients or elderly patients with compromised renal function) the co-administration of an ACE inhibitor or Angiotensin II antagonist and agents that inhibit cyclo-oxygenase may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. These interactions should be considered in patients taking a coxib concomitantly with ACE inhibitors or angiotensin II antagonists. Therefore, the combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy, and periodically thereafter. Diuretics can increase

the risk of nephrotoxicity. Phenylephrine may reduce the efficacy of beta-blockers and antihypertensives. The risk of hypertension and other cardiovascular side effects may be increased (see section 4.3).

Corticosteroids

Increased risk of gastrointestinal ulceration or bleeding (see section 4.4).

Anti-platelet agents and selective serotonin-reuptake inhibitors (SSRIs)

Increased risk of gastrointestinal bleeding (see section 4.4).

Digoxin and cardiac glycosides

NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma glycoside levels. Concomitant use of phenylephrine may increase the risk of irregular heartbeat or heart attack.

Tricyclic antidepressants (e.g. amitriptyline)

May increase the risk of cardiovascular side effects with phenylephrine (see section 4.3).

Sympathomimetic amines

Concomitant use of phenylephrine with other sympathomimetic amines can increase the risk of cardiovascular side effects.

Lithium

There is evidence for potential increase in plasma levels of lithium.

Methotrexate

There is potential for an increase in plasma methotrexate.

Ciclosporin

Increased risk of nephrotoxicity.

Mifepristone

NSAIDs should not be used for 8-12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone.

Tacrolimus

Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus.

Zidovudine

Increased risk of haematological toxicity when NSAIDs are given with zidovudine. There is evidence of an increased risk of haemarthroses and haematoma in HIV(+) haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.

Quinolone antibiotics

Animal data indicate that NSAIDs can increase the risk of convulsions associated with quinolone antibiotics. Patients taking NSAIDs and quinolones may have an increased risk of developing convulsions.

4.6 Fertility, pregnancy and lactation

The use of this medicine should be avoided during the first six months of pregnancy and is contraindicated in the last three months of pregnancy.

This medicine should not be used during breast-feeding.

Ibuprofen

Pregnancy

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development.

Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1 %, up to approximately 1.5 %. The risk is believed to increase with dose and duration of therapy.

In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-foetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period.

From the 20th week of pregnancy onward, ibuprofen use may cause oligohydramnios resulting from foetal dysfunction. This may occur shortly after treatment initiation and is usually reversible upon discontinuation. In addition, there have been reports of ductus arteriosus constriction following treatment in the second trimester, most of which resolved after treatment cessation. Therefore, during the first and second trimester of pregnancy, ibuprofen should not be given unless clearly necessary. If ibuprofen is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible. Antenatal monitoring for oligohydramnios and ductus arteriosus constriction should be considered after exposure to ibuprofen for several days from gestational week 20 onward. Ibuprofen should be discontinued if oligohydramnios or ductus arteriosus constriction are found.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to:

- cardiopulmonary toxicity (premature constriction/closure of the ductus arteriosus and pulmonary hypertension);
- renal dysfunction (see above);

the mother and the neonate, at the end of the pregnancy, to:

- possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses;
- inhibition of uterine contractions resulting in delayed or prolonged labour.

Consequently, ibuprofen is contraindicated during the third trimester of pregnancy (see sections 4.3 and 5.3).

Breast-feeding

Ibuprofen and its metabolites pass only in low concentrations into the breast milk. Since harmful effects to infants have not become known to date, an interruption of breastfeeding is usually not necessary during short-term treatment with ibuprofen at the recommended dose.

Fertility

Impaired female fertility: There is limited evidence that drugs which inhibit cyclo-oxygenase/prostaglandin synthesis may cause impairment of female fertility by an effect on ovulation. This is reversible on withdrawal of treatment.

Phenylephrine

Pregnancy

The safety of this medicine during pregnancy has not been established but in view of a possible association of foetal abnormalities with first trimester exposure to phenylephrine and due to the vasoconstrictive properties of phenylephrine the product should be used with caution in patients with history of pre-eclampsia. Phenylephrine may reduce placental perfusion and until more information is available, **use of phenylephrine should be avoided during pregnancy**.

Breast-feeding

The safety of this medicine during lactation has not been established.

Animal data indicate that phenylephrine can decrease milk production, and therefore **this medicine should not be used during breast feeding**.

Fertility

The effects of phenylephrine on male or female fertility have not been studied.

4.7 Effects on ability to drive and use machines

No adverse effects known.

4.8 Undesirable effects

Summary of the safety profile

The most commonly observed adverse events are gastrointestinal in nature.

Hypersensitivity reactions have been reported following treatment with ibuprofen and these may consist of:

(a) Non-specific allergic reaction and anaphylaxis.

(b) Respiratory tract reactivity, e.g. asthma, aggravated asthma, bronchospasm or dyspnoea.

(c) Various skin reactions, e.g. pruritis, urticaria, angioedema and, more rarely, exfoliative and bullous dermatoses (including epidermal necrolysis and erythema multiforme).

The following list of adverse effects relates to those experienced with ibuprofen at OTC doses, for short-term use. In the treatment of chronic conditions, under long-term treatment, additional effects may occur.

Tabulated summary of adverse reactions

The incidences of undesirable effects are tabulated below. They are listed by system organ class and frequency 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)

Ibuprofen

Blood and lymphatic system disorders

Very rare: Haematopoietic disorders (anaemia, leucopenia, thrombocytopenia, pancytopenia, agranulocytosis). First signs are: fever, sore throat, superficial mouth ulcers, flu-like symptoms, severe exhaustion, unexplained bleeding and bruising.

Immune system disorders

In patients with existing auto-immune disorders (such as systemic lupus erythematosus, mixed connective tissue disease) during treatment with ibuprofen, single cases of symptoms of aseptic meningitis, such as stiff neck, headache, nausea, vomiting, fever or disorientation, have been observed (see section 4.4).

Hypersensitivity reactions

Uncommon: Hypersensitivity reactions with urticaria and pruritus.

Very rare: Severe hypersensitivity reactions. Symptoms could be: facial, tongue and laryngeal swelling, dyspnoea, tachycardia, hypotension (anaphylaxis, angioedema or severe shock).

Exacerbation of asthma and bronchospasm.

Nervous system disorders

Uncommon: Headache, dizziness and tinnitus.

Very rare: Aseptic meningitis - single cases have been reported very rarely.

Cardiac disorders

Oedema, hypertension and cardiac failure have been reported in association with NSAID treatment.

Clinical studies suggest that use of ibuprofen, particularly at a high dose (2400 mg/day) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke) (see section 4.4).

Gastrointestinal disorders

Uncommon: Abdominal pain, nausea and dyspepsia.

Rare: Diarrhoea, flatulence, constipation and vomiting.

Very rare: Peptic ulcer, perforation and gastrointestinal haemorrhage, melaena, haematemesis, sometimes fatal, particularly in the elderly. Ulcerative stomatitis, gastritis and mouth ulceration.

Exacerbation of colitis and Crohn's disease (see section 4.4).

Hepatobiliary disorders

Very rare: Liver disorders.

Skin and subcutaneous tissue disorders

Uncommon: Various skin rashes.

Very rare: Severe forms of skin reactions such as bullous reactions, including Stevens-Johnson Syndrome, erythema multiforme and toxic epidermal necrolysis, can occur.

Not known: Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome), acute generalised exanthematous pustulosis (AGEP), photosensitivity reactions.

Renal and urinary disorders

Very rare: Acute renal failure, papillary necrosis, especially in long-term use, associated with increased serum urea and oedema.

<u>Phenylephrine</u>

High blood pressure with headache and vomiting, probably only in overdose. Rarely, palpitations.

Also, rare reports of allergic reactions and occasionally urinary retention in males.

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 wwww.mhra.gov.uk/yellowcard or search for 'MHRA Yellow Card' in the Google Play or Apple App Store.

4.9 Overdose

Ibuprofen

In children, ingestion of more than 400 mg/kg may cause symptoms. In adults, the dose response rate effect is less clear cut. The half-life in overdose is 1.5-3 hours.

Symptoms

Patients who have ingested clinically important amounts of NSAIDs will develop no more than nausea, vomiting, epigastric pain, or more rarely diarrhoea. Tinnitus, headache and gastrointestinal bleeding are also possible. In more serious poisoning, toxicity is seen in the central nervous system, manifesting as drowsiness, occasionally excitation and disorientation or coma. Occasionally patients develop convulsions. In serious poisoning hyperkalaemia and/or metabolic acidosis may occur and prothrombin time/INR may be prolonged, probably due to interference with the actions of circulating clotting factors. Acute renal failure and liver damage may occur. Exacerbation of asthma is possible in asthmatics. Prolonged use at higher than recommended doses or overdose may result in renal tubular acidosis and hypokalaemia.

Management

Management should be symptomatic and supportive and include the maintenance of a clear airway and monitoring of cardiac and vital signs until stable. Consider oral administration of activated charcoal if the patient presents within 1 hour of ingestion of a potentially toxic amount. If frequent or prolonged, convulsions should be treated with intravenous diazepam or lorazepam. Give bronchodilators for asthma.

Phenylephrine

Features of severe overdose of phenylephrine include haemodynamic changes and cardiovascular collapse with respiratory depression.

Treatment includes early gastric lavage and symptomatic and supportive measures. Hypertensive effects may be treated with an intravenous alpha-receptor blocking agent.

Phenylephrine overdose is likely to result in: nervousness, headache, dizziness, insomnia, increased blood pressure, nausea, vomiting, mydriasis, acute angle closure glaucoma (most likely to occur in those with closed angle glaucoma), tachycardia, palpitations, allergic reactions (e.g. rash, urticaria, allergic dermatitis), dysuria, urinary retention (most likely to occur in those with bladder outlet obstruction, such as prostatic hypertrophy).

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiinflammatory and antirheumatic products, propionic acid derivatives

ATC-code: M01AE51

Ibuprofen

Ibuprofen is a propionic acid derivative NSAID that has demonstrated its efficacy by inhibition of prostaglandin synthesis. In humans ibuprofen reduces inflammatory pain, swellings and fever. Furthermore, ibuprofen reversibly inhibits platelet aggregation.

The therapeutic effect of ibuprofen in symptoms relating to the common cold and influenza has a duration of up to 8 hours.

Experimental data suggest that ibuprofen may competitively inhibit the effect of low dose acetylsalicylic acid on platelet aggregation when they are dosed concomitantly. Some pharmacodynamic studies show that when single doses of ibuprofen 400 mg were taken within 8 h before or within 30 min after immediate release acetylsalicylic acid dosing (81 mg), a decreased effect of acetylsalicylic acid on the formation of thromboxane or platelet aggregation occurred. Although there are uncertainties regarding extrapolation of these data to the clinical situation, the possibility that regular, long-term use of ibuprofen may reduce the cardioprotective effect of low-dose acetylsalicylic acid cannot be excluded. No clinically relevant effect is considered to be likely for occasional ibuprofen use (see section 4.5).

Phenylephrine

Phenylephrine is a post-synaptic alpha-receptor agonist with low cardioselective beta-receptor affinity and minimal central stimulant activity. It is a recognised decongestant and acts by vasoconstriction to reduce oedema and nasal swelling.

5.2 Pharmacokinetic properties

Ibuprofen

Ibuprofen is rapidly absorbed following administration and is rapidly distributed throughout the whole body. The excretion is rapid and complete via the kidneys.

Maximum plasma concentrations are reached 45 minutes after ingestion if taken on an empty stomach. When taken with food, peak levels are observed after 1-2 hours. These times may vary with different dosage forms.

The half-life of ibuprofen is about 2 hours.

In limited studies, ibuprofen appears in the breast milk in very low concentrations.

Phenylephrine

Phenylephrine is absorbed from the gastrointestinal tract, but has reduced bioavailability by the oral route due to first-pass metabolism.

It retains activity as a nasal decongestant when given orally, the drug distributing through the systemic circulation to the vascular bed of the nasal mucosa.

When taken by mouth as a nasal decongestant, phenylephrine is usually given at intervals of 4-6 hours.

Ibuprofen and phenylephrine combination

The ibuprofen component of a fixed combination (ibuprofen 200 mg plus phenylephrine hydrochloride 5 mg) is absorbed faster than standard ibuprofen 200 mg tablets, with therapeutic levels being reached in 26.4 minutes (from the fixed combination) as opposed to 55.2 minutes (for standard ibuprofen).

5.3 Preclinical safety data

There are no findings of relevance to the prescriber other than those already mentioned elsewhere in the SmPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

- Microcrystalline Cellulose
- Sodium starch glycolate type A
- Hypromellose 6 mPa.s
- Sodium stearyl fumarate

Film:

Opadry white 200F280000 (consisting of polyvinyl alcohol, talc, macrogol 4000, titanium dioxide (E171), Methacrylic acid – ethyl acrylate copolymer 1:1 (Type A), sodium bicarbonate)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Do not store above 30°C

6.5 Nature and contents of container

PVC/PE/PVdC - AL blister

Blister: 10, 12, 16, 20, 24 tablets

Not all pack sizes may be marketed

6.6 Special precautions for disposal

Not applicable.

7 MARKETING AUTHORISATION HOLDER

Thornton & Ross Ltd.

Linthwaite,

Huddersfield,

HD7 5QH, UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 00240/0393

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