SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

DYPRACET 20 mg/500 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

DYPRACET 20 mg/500 mg Tablets contain Paracetamol 500 mg and Dihydrocodeine Tartrate 20 mg.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

DYPRACET 20 mg/500 mg Tablets are oblong, white tablets, 19 mm x 7 mm long with the marking P500 D20 on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

DYPRACET 20 mg/500 mg Tablets: For the treatment of severe pain.

4.2 Posology and method of administration

Prior to starting treatment with opioids, a discussion should be held with patients to put in place a strategy for ending treatment with dihydrocodeine tartrate in order to minimise the risk of addiction and drug withdrawal syndrome (see section 4.4).

<u>Posology</u>

Adults over 18 years

1 or 2 tablets every four to six hours.

Do not exceed 8 tablets in any 24-hour period.

Paediatric population

Adolescents 16-18 years
1 or 2 tablets every six hours when necessary up to a maximum of 8 tablets in any 24-hour period.

Children 12-15 years
1 tablet every six hours when necessary up to a maximum of 4 tablets in any 24-hour period.

Children under 12 years

Not recommended.

Elderly

1 tablet every four to six hours increasing to 2 tablets every four to six hours if required and tolerated. Caution should be exercised when increasing the dose in the elderly.

Method of administration

Oral.
DYPRACET 20 mg/500 mg tablets should, if possible, be taken during or after meals.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in 6.1.

Respiratory depression.

Obstructive airways disease

4.4 Special warnings and precautions for use

DYPRACET Tablets should be given with caution in patients with allergic disorders and should not be given during an attack of asthma. Caution should also be observed if there is marked impairment of liver function, advanced kidney disease and in chronic alcoholics.

Do not exceed the recommended dose.

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

Risk from concomitant use of sedative medicines such as benzodiazepines or related drugs:
Concomitant use of DYPRACET Tablets and sedative medicines such as benzodiazepines or related drugs may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing with these sedative medicines should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe DYPRACET Tablets concomitantly with sedative medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible.

The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their caregivers to be aware of these symptoms (see section 4.5).

Dosage should be reduced in the elderly, in hypothyroidism and in chronic hepatic disease. An overdose can cause hepatic necrosis.

Dihydrocodeine should be used with caution in patients taking monoamine oxidase inhibitors and should be avoided in those patients with raised intracranial pressure or head injury.

Use with caution in patients with prostatic hypertrophy since dihydrocodeine may cause urinary retention.

The risk-benefit of continued use should be assessed regularly by the prescriber, and in particular the prescriber should take care to avoid any unnecessary increase in dosage especially where there is evidence of a previous history of drug dependence or abuse.

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.

Drug dependence, tolerance and potential for abuse

For all patients, prolonged use of this product may lead to drug dependence (addiction), even at therapeutic doses. The risks are increased in individuals with current or past history of substance misuse disorder (including alcohol misuse) or mental health disorder (e.g., major depression).
Additional support and monitoring may be necessary when prescribing for patients at risk of opioid misuse.

A comprehensive patient history should be taken to document concomitant medications, including over-the-counter medicines and medicines obtained on-line, and past and present medical and psychiatric conditions.
Patients may find that treatment is less effective with chronic use and express a need to increase the dose to obtain the same level of pain control as initially experienced. Patients may also supplement their treatment with additional pain relievers. These could be signs that the patient is developing tolerance. The risks of developing tolerance should be explained to the patient.

Overuse or misuse may result in overdose and/or death. It is important that patients only use medicines that are prescribed for them at the dose they have been prescribed and do not give this medicine to anyone else.

Patients should be closely monitored for signs of misuse, abuse, or addiction. The clinical need for analgesic treatment should be reviewed regularly.

Drug withdrawal syndrome

Prior to starting treatment with any opioids, a discussion should be held with patients to put in place a withdrawal strategy for ending treatment with dihydrocodeine tartrate.

Drug withdrawal syndrome may occur upon abrupt cessation of therapy or dose reduction. When a patient no longer requires therapy, it is advisable to taper the dose gradually to minimise symptoms of withdrawal. Tapering from a high dose may take weeks to months.

The opioid drug withdrawal syndrome is characterised by some or all of the following: restlessness, lacrimation, rhinorrhoea, yawning, perspiration, chills, myalgia, mydriasis and palpitations. Other symptoms may also develop including irritability, agitation, anxiety, hyperkinesia, tremor, weakness, insomnia, anorexia, abdominal cramps, nausea, vomiting, diarrhoea, increased blood pressure, increased respiratory rate or heart rate.

Tolerance diminishes rapidly after withdrawal so a previously tolerated dose may prove fatal.

If women take this drug during pregnancy, there is a risk that their newborn infants will experience neonatal withdrawal syndrome.
Prolonged use of a painkiller for headaches can make them worse.

Hyperalgesia

Hyperalgesia may be diagnosed if the patient on long-term opioid therapy presents with increased pain. This might be qualitatively and anatomically distinct from pain related to disease progression or to breakthrough pain resulting from development of opioid tolerance. Pain associated with hyperalgesia tends to be more diffuse than the pre-existing pain and less defined in quality. Symptoms of hyperalgesia may resolve with a reduction of opioid dose.

4.5 Interaction with other medicinal products and other forms of interaction

Additive CNS depression may occur with alcohol, and other CNS depressants such as anxiolytics, anti-depressants, hypnotics and anti-psychotics. The rate of absorption of paracetamol may be increased by metoclopramide or domperidone and absorption of paracetamol may be reduced by cholestyramine.

The anti-coagulant effect of warfarin and other coumarins may be enhanced by prolonged regular use of paracetamol with increased risk of bleeding.

Sedative medicines such as benzodiazepines or related drugs:
The concomitant use of opioids with sedative medicines such as benzodiazepines or related drugs increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dose and duration of concomitant use should be limited (see section 4.4).

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).

4.6 Fertility, pregnancy and lactation

Pregnancy
Epidemiological studies in human pregnancy have shown no effects due to paracetamol or dihydrocodeine. However, both drugs should be avoided during pregnancy unless considered essential by the physician.

Regular use during pregnancy may cause drug dependence in the foetus, leading to withdrawal symptoms in the neonate.

If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Administration during labour may depress respiration in the neonate and an antidote for the child should be readily available.

A large amount of data on pregnant women indicate neither malformative, nor foeto/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.

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

Administration to nursing women is not recommended as dihydrocodeine tartrate may be secreted in breast milk and may cause respiratory depression in the infant.

If the patient is an ultra-rapid metaboliser of CYP2D6, higher levels of codeine may be present in breast milk and on very rare occasions may result in symptoms of opioid toxicity in the infant.

If symptoms of opioid toxicity develop in either the mother or the infant, then all codeine containing medicines should be stopped and alternative non-opioid analgesics prescribed. In severe cases consideration should be given to prescribing naloxone to reverse these effects.

Fertility
There are insufficient fertility data available to indicate whether paracetamol or dihydrocodeine has any effect on fertility.

4.7 Effects on ability to drive and use machines

Dihydrocodeine may cause drowsiness and, if affected, patients should not drive or operate machinery.

This medicine can impair cognitive function and can affect a patient's ability to drive safely. This class of medicine is in the list of drugs included in regulations under 5a of the Road Traffic Act 1988. When prescribing this medicine, patients should be told:

- The medicine is likely to affect your ability to drive
- Do not drive until you know how the medicine affects you
- It is an offence to drive while under the influence of this medicine
- However, you would not be committing an offence (called "statutory defence") if:
  - The medicine has been prescribed to treat a medical or dental problem and
  - You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and It was not affecting your ability to drive safely.

4.8 Undesirable effects

Prolonged use of a painkiller can make conditions such as headache worse.

Paracetamol
Adverse effects of paracetamol are rare but hypersensitivity reactions including skin rash, blood dyscrasias, acute pancreatitis have been reported. Very rare cases of serious skin reactions have been reported.

Metabolism and nutrition disorders
Not known: High anion gap metabolic acidosis.

Dependence may occur. Regular prolonged use of dihydrocodeine is known to lead to addiction and tolerance. Symptoms of restlessness and irritability may result when treatment is then stopped.

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.

Dihydrocodeine
Constipation, if it occurs, is readily treated with a mild laxative.

Other side-effects of dihydrocodeine, which may occur in a few patients, are nausea, vomiting, headache, vertigo, giddiness, urinary retention, pruritus, sedation, dysphoria, hallucinations, abdominal pain and allergic reactions including skin rashes.

Unknown frequency: Drug dependence (see section 4.4).
Uncommon frequency: Drug withdrawal syndrome.

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 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, 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 depleted 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.

Management

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 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.

Dihydrocodeine

Patients should be informed of the signs and symptoms of overdose and to ensure that family and friends are also aware of these signs and to seek immediate medical help if they occur.

Symptoms

Acute overdosage with dihydrocodeine can be manifested by somnolence progressing to stupor or coma, miotic pupils, rhabdomyolysis, non-cardiac pulmonary oedema, bradycardia, hypotension and respiratory depression or apnoea.

Management

Primary attention should be given to the establishment of a patent airway and institution of assisted or controlled ventilation.

In the case of massive overdosage, administer naloxone intravenously (0.4 to 2 mg for an adult and 0.01 mg/kg body weight for children) if the patient is in a coma or respiratory depression is present. Repeat the dose at 2 minute intervals if there is no response, or by an infusion. An infusion of 60% of the initial dose per hour is a useful starting point. A solution of 10 mg made up in 50 ml dextrose will produce 200 micrograms/ml for infusion using an IV pump (dose adjusted to the clinical response). Infusions are not a substitute for frequent review of the patient's clinical state. Intramuscular naloxone is an alternative in the event that IV access is not possible.

As the duration of action of naloxone is relatively short, the patient must be carefully monitored until spontaneous respiration is reliably re-established. Naloxone is a competitive antagonist and large doses (4 mg) may be required in seriously poisoned patients. For less severe overdosage, administer naloxone 0.2 mg intravenously followed by increments of 0.1 mg every 2 minutes if required.

Naloxone should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to dihydrocodeine overdosage. Naloxone should be administered cautiously to persons who are known, or suspected, to be physically dependent on dihydrocodeine. In such cases, an abrupt or complete reversal of opioid effects may precipitate pain and an acute withdrawal syndrome.

Consider activated charcoal (50 g for adults, 10-15 g for children), if a substantial amount has been ingested within 1 hour, provided the airway can be protected.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Analgesics, Opioids in combination with non-opioid analgesics, ATC code: N02AJ01

Paracetamol is an effective analgesic possessing a remarkably low level of side effects. Its broad clinical utility has been extensively reported, and it now largely replaces aspirin for routine use. Paracetamol is well tolerated; having a bland effect on gastric mucosa, unlike aspirin, it neither exacerbates symptoms of peptic ulcer nor precipitates bleeding. Dihydrocodeine tartrate has been widely used for a number of years as a powerful analgesic.

In addition the compound exhibits well-defined anti-tussive activity.

Fortifying paracetamol with dihydrocodeine tartrate provides an effective combination of drugs for the treatment of severe pain.

5.2 Pharmacokinetic properties

Dihydrocodeine is well absorbed from the gastrointestinal tract. Like other phenanthrene derivatives, dihydrocodeine is mainly metabolised in the liver with the resultant metabolites being excreted mainly in the urine.

Metabolism of dihydrocodeine includes 0-demethylation, N-demethylation and 6-keto reduction.

Paracetamol is readily absorbed from the gastrointestinal tract with peak plasma concentrations occurring 30 minutes to 2 hours after ingestion. It is metabolised in the liver and excreted in the urine as the glucuronide and sulphate conjugates.

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose
Povidone K30
Colloidal anhydrous silica

Magnesium stearate

6.2 Incompatibilities

None known.

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

DYPRACET 20 mg/500 mg Tablets are available in HDPE containers with polypropylene lids containing 56 or 112 tablets or in PVC foiled aluminium blisters containing 56 or 112 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

PL 20075/1006

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