Public Assessment Report

Decentralised Procedure

DYPRACET 20 MG/500 MG AND 30 MG/500 MG TABLETS

DIHYDROCODEINE HYDROGEN TARTRATE PARACETAMOL

UK/H/4104/001-2/DC

UK Licence No: PL 17507/0151-2

AUDEN MCKENZIE LIMITED
LAY SUMMARY

On 21st March 2012, the UK granted Auden McKenzie Limited Marketing Authorisations (licences) for Dypracet 20 mg/500 mg and 30 mg/500 mg Tablets.

Dypracet 20 mg/500 mg and 30 mg/500 mg Tablets contain the drug ingredients, dihydrocodeine hydrogen tartrate and paracetamol which belong to a group of medicines called strong analgesics or ‘painkillers’.

Dypracet 20 mg/500 mg and 30 mg/500 mg Tablets are used to relieve severe pain over a period of 4 to 6 hours.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Dypracet 20 mg/500 mg and 30 mg/500 mg Tablets outweigh the risks; hence these Marketing Authorisations have been granted.
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Module 6: Steps taken after initial procedure        Not applicable
# Module 1

| Product Name               | Dypracet 20 mg/500 mg Tablets  
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<th>Dypracet 30 mg/500 mg Tablets</th>
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<td>Type of Application</td>
<td>Generic application, Article 10(1)</td>
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| Drug Substance             | Dihydrocodeine hydrogen tartrate  
|                           | Paracetamol                      |
| Form                       | Tablet                          |
| Strength                   | 20 mg dihydrocodeine hydrogen tartrate/500 mg paracetamol  
|                           | 30 mg dihydrocodeine hydrogen tartrate/500 mg paracetamol |
| MA Holder                  | Auden Mckenzie (Pharma Division) Ltd  
|                           | McKenzie House                   |
|                           | Bury Street                      |
|                           | Ruislip                          |
|                           | Middlesex                        |
|                           | HA4 7TL                          |
|                           | United Kingdom.                  |
| Reference Member State (RMS) | United Kingdom (UK)              |
| Concerned Member States (CMS) | Ireland (IE)                    |
| Procedure Number           | UK/H/4104/001/DC                  |
|                           | UK/H/4104/002/DC                  |
| End of Procedure           | Day 207: 20th February 2012      |
Module 2
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 a 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
Route of Administration
Oral.
DYPRACET 20 mg/500 mg Tablets should, if possible, be taken during or after meals.

Adults and children over 12 years
1 or 2 tablets every four to six hours.
Do not exceed eight tablets in any 24-hour period.

Children under 12 years
Not recommended.

Elderly
One tablet every 4 - 6 hours increasing to two tablets every 4 - 6 hours if required and tolerated.
Caution should be exercised when increasing the dose in the elderly.

4.3 Contraindications
Respiratory depression, obstructive airways disease, hypersensitivity to paracetamol, dihydrocodeine or other tablet constituents.

4.4 Special warnings and precautions for use
DYPRACET 20 mg/500 mg 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.

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.
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.

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.

Lactation

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

At normal therapeutic doses codeine may be present in breast milk at very low doses and is unlikely to adversely affect the breast fed infant.

However, 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 nalaxone 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.

4.8 Undesirable effects

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 and allergic reactions including skin rashes.

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

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.

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

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.
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
Symptoms
Acute overdosage with dihydrocodeine can be manifested by somnolence progressing to stupor or coma, miosis 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
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
24 months

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
Auden Mckenzie (Pharma Division) Ltd
McKenzie House
Bury Street
Ruislip
Middlesex
HA4 7TL
UK

8  MARKETING AUTHORISATION NUMBER(S)
   PL 17507/0151

9  DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
   21/03/2012

10 DATE OF REVISION OF THE TEXT
   21/03/2012
1 NAME OF THE MEDICINAL PRODUCT
DYPRACET 30 mg/500 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
DYPRACET 30 mg/500 mg Tablets contain Paracetamol 500 mg and Dihydrocodeine Tartrate 30 mg.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Tablet
DYPRACET 30 mg/500 mg Tablets are oblong, white tablets, 19 mm x 7 mm long with the marking P500 D30 on one side.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
DYPRACET 30 mg/500 mg Tablets: For the treatment of severe pain where there is a higher analgesic requirement.

4.2 Posology and method of administration
Route of Administration
Oral.
DYPRACET 30 mg/500 mg Tablets should, if possible, be taken during or after meals.

Adults and children over 12 years
1 or 2 tablets every four to six hours.
Do not exceed eight tablets in any 24-hour period.

Children under 12 years
Not recommended.

Elderly
One tablet every 4 - 6 hours increasing to two tablets every 4 - 6 hours if required and tolerated.
Caution should be exercised when increasing the dose in the elderly.

4.3 Contraindications
Respiratory depression, obstructive airways disease, hypersensitivity to paracetamol, dihydrocodeine or other tablet constituents.

4.4 Special warnings and precautions for use
DYPRACET 30 mg/500 mg 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.

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.

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

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.

Lactation

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

At normal therapeutic doses codeine may be present in breast milk at very low doses and is unlikely to adversely affect the breast fed infant.

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Or

b) Regularly consumes ethanol in excess of recommended amounts.
c) Is likely to be glutathione depleted e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia.

**Symptoms**
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**Dihydrocodeine**

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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.

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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.

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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
24 months

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container
DYPRACET 30 mg/500 mg Tablets are available in HDPE containers with polypropylene lids containing 56 tablets or in PVC foiled aluminium blisters containing 56 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Auden Mckenzie (Pharma Division) Ltd
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<td>21/03/2012</td>
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Module 3
Product Information Leaflets

Read all of this leaflet carefully because it contains important information for you.
1. Keep this leaflet. You may need to read it again.
2. If you have any further questions, ask your doctor or pharmacist.
3. This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
4. If any of the side effects become serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

- This medicine contains paracetamol.
- Do not take any other paracetamol containing products.
- Do not exceed the stated dose.
- Immediate medical advice should be sought in the event of overdosage because of the risk of irreversible liver damage.

In this leaflet
1. What are DYPRACET Tablets and what are they used for?
2. Before you take DYPRACET Tablets
3. How to take DYPRACET Tablets
4. Possible side effects
5. Storing DYPRACET Tablets
6. Further information

1. What are DYPRACET Tablets and what are they used for?

The name of this medicine is DYPRACET 20 mg/500 mg & DYPRACET 30 mg/500 mg Tablets. These tablets have been prescribed for you to relieve severe pain over a period of 4 to 6 hours. They contain the active ingredients dihydrocodeine tartrate and paracetamol which belong to a group of medicines called strong analgesics or ‘painkillers’.

The other ingredients are listed in section 6 of this leaflet.

2. Before you take DYPRACET Tablets

Do not take DYPRACET Tablets if you are:
- Are allergic (hypersensitive) to dihydrocodeine, paracetamol or any of the other ingredients of the tablets (see section 6 ‘Further Information’);
- Have breathing problems, such as breathing more slowly or weakly than expected, or obstructive airways disease;
- Are having an asthma attack.

Children under 12 years of age should not take these tablets.

Special Precautions
Check with your doctor or pharmacist before taking your medicine if you suffer from any of the following:
- Have asthma or any allergies;
- Have an under-active thyroid gland (hypothyroidism);
- Have kidney or long-term liver problems;
- Have a severe headache or feel sick due to a head injury or increased pressure in your skull (for instance due to brain disease). This is because the tablets may make these symptoms worse or hide the extent of a head injury;
- Have prostate problems;
- Are addicted to alcohol;
- Are or have ever been addicted to drugs.

If you are not sure if any of the above applies to you, talk to your doctor or pharmacist before taking this medicine.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. Taking some medicines together can be harmful.

In particular, tell your doctor or pharmacist if you are taking any of the following medicines:
- Any other medicines containing paracetamol (you should not take these tablets if you are already taking another medicine containing paracetamol);
- Medicines to help you sleep (for example tranquillisers, hypnotics or sedatives);
- Medicines to treat psychiatric or mental disorders;
- A type of medicine known as a monoamine oxidase inhibitor (examples include tranylcypromine, phenelzine, isocarboxazid, moclobemide and linezolid), or you have taken this type of medicine in the last two weeks;
- Medicines to treat depression or anxiety;
- Metoclopramide or domperidone to stop you feeling or being sick;
- Cholestyramine to treat high blood pressure or diarrhoea;
- Medicines such as warfarin to prevent your blood clotting or to help thin your blood.

If you are unsure of the types of medicines you are taking, ask your doctor or pharmacist.

Taking DYPRACET with alcohol
Drinking alcohol during your treatment with these tablets may make you sleepy. If you are affected you should avoid drinking alcohol.

Pregnancy and breast feeding
If you are pregnant or breast feeding do not take these tablets until you have spoken to your doctor.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
You may feel sleepy when taking these tablets. If you are affected you should not drive or use machinery.

3. How to take DYPRACET Tablets

Two different strengths of tablets are available. Your doctor will decide which strength of tablet will suit you best. Always take this medicine exactly as your doctor or pharmacist has told you. You should check with them if you are not sure. DYPRACET should be taken orally. The tablets should be swallowed whole with a glass of water.

Adults and children 12 years or over:
The usual starting dose for adults and children over 12 years of age is one or two tablets every 4 to 6 hours.

Your doctor will prescribe the dose required to treat your pain. If you find that you are still in pain whilst taking these tablets discuss this with your doctor.
Do not take more than eight tablets in 24 hours.
Do not take these tablets if you are already taking another medication containing paracetamol.

Elderly:
If you are elderly your doctor may suggest a lower starting dose.

Children under 12 years of age:
This product should not be taken by children under 12 years of age.

If you take more DYPRACET Tablets than you should:
Call your doctor or hospital straight away. People who have taken an overdose may feel very sleepy and sick, and have abdominal pain. They may also have breathing difficulties leading to unconsciousness or even death and may need emergency treatment in hospital. You should contact your doctor immediately even if you feel well as there is a risk of serious liver damage.

When seeking medical attention make sure that you take this leaflet and any remaining tablets with you to show the doctor.

If you forget to take DYPRACET Tablets:
If you miss a dose you should take it as soon as you remember and then carry on as before. Do not take a double dose to make up for a forgotten tablet.

If you stop taking DYPRACET Tablets:
You should not stop taking these tablets unless your doctor tells you to. If you want to stop taking your tablets, discuss this with your doctor first.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, DYPRACET Tablets can have side effects, although not everybody gets them.

To give you an idea of how many patients might get side effects, they have been listed as very common, common, uncommon, rare and very rare. These mean the following:

<table>
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<tr>
<th>Side Effect</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common</td>
<td>More than 1 in 10 people.</td>
</tr>
<tr>
<td>Common</td>
<td>up to 1 in 10 people.</td>
</tr>
<tr>
<td>Uncommon</td>
<td>up to 1 in 100 people.</td>
</tr>
<tr>
<td>Rare</td>
<td>up to 1 in 1,000 people.</td>
</tr>
<tr>
<td>Very rare</td>
<td>fewer than 1 in 10,000 people.</td>
</tr>
</tbody>
</table>

- **Common:**
  - Most people will have constipation when they take these tablets. Your doctor can prescribe a laxative to overcome this problem.
  - You may feel sick or vomit (be sick) when you take your tablets, this should normally wear off after a few days however your doctor can prescribe an anti-vomiting medicine if it continues to be a problem.
  - You may find that you feel more sleepy than normal when you start taking your tablets or when your dose is increased. This should wear off after a few days.
  - Headache and a rash or itchy skin have also been commonly reported in patients treated with these tablets.

- **Uncommon:**
  - An unpleasant or uncomfortable mood.
  - Hallucinations.
  - A feeling of dizziness or 'spinning'.
  - Difficulty in passing urine.
  - A need to take increasingly higher doses to obtain the same level of pain relief (tolerance).
  - Withdrawal symptoms such as agitation, anxiety, shaking or sweating upon stopping taking the tablets.

- **Rare:**
  - Inflammation of the pancreas (which causes severe pain in the abdomen and back).
  - Abnormal cells in the blood (blood dyscrasias).

Contact your doctor or pharmacist immediately if you experience any sudden wheeziness, difficulties in breathing, swelling of the eyelids, face or lips, rash or itching especially those covering your whole body as these may indicate an allergy to the product.

As with all strong painkillers, there is a risk you may become addicted or reliant on these tablets.

Taking a painkiller for headaches too often or for too long can make your headaches worse.

If any of the above side effects are troublesome or last more than a few days or if you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

5. Storing DYPRACET Tablets

Keep all medicines out of the reach and sight of children.

There are no special storage instructions for DYPRACET Tablets.

Do not use DYPRACET after the expiry date on the carton, blister and pot container. The expiry date refers to the last day of that month.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. Further Information

What DYPRACET Tablets contain:
The active ingredients are paracetamol and dihydrocodeine tartrate.

Each Dypracet 20 mg/500 mg Tablet contains paracetamol 500 mg and dihydrocodeine tartrate 20 mg.

Each Dypracet 30 mg/500 mg Tablet contains paracetamol 500 mg and dihydrocodeine tartrate 30 mg.

The tablets also contain microcrystalline cellulose, povidone K30, colloidal anhydrous silica and magnesium stearate.

What DYPRACET looks like and contents of the pack:

Dypracet 20 mg/500 mg Tablets are oblong, white tablets, 19 mm x 7 mm long with the marking 'PS00 D20' on one side.

Dypracet 30 mg/500 mg Tablets are oblong, white tablets, 19 mm x 7 mm long with the marking 'PS00 D30' on one side.

Dypracet 20 mg/500 mg Tablets are available in pots of 56 or 112 tablets and in blister packs of 56 tablets.

Dypracet 30 mg/500 mg Tablets are available in pots of 56 tablets and blister packs of 56 tablets.

Not all pack sizes may be marketed.

Marketing authorisation holder:
Auden Mckenzie (Pharma Division) Ltd.
Mckenzie House, Bury Street,
Ruislip, Middlesex, HA4 7TJ, UK

Manufacturer:
Tiofarma B.V.
Benjamin Franklinstraat 7-9,
3261 LW Oud-Beijerland,
The Netherlands

This leaflet was last approved in March 2012.

For information in large print, on tape, on CD or in Braille, phone +44 (0)1895 627 420.
Dypracet® 20 mg/500 mg Tablets
(Dihydrocodeine Tartrate 20 mg & Paracetamol 500 mg)

56 tablets

Each tablet contains Paracetamol 500 mg and Dihydrocodeine Tartrate 20 mg.

For oral use only.

Please read the enclosed package leaflet before use.

KEEP MEDICINES OUT OF THE REACH AND SIGHT OF CHILDREN

Medicinal product subject to medical prescription.

Contains paracetamol. Immediate medical advice should be sought in the event of an overdose, even if you feel well.

Do not take with any other paracetamol containing products.

PL No. 12987/031 - PA 1385/19/1
Product Licence Holder: Auden McKenzie (Pharma Division) Ltd. Mckenzie House, Bury Street, Bury, Bury BL8 4NL, UK.

B/N XXXX
Exp xx/yyyy

20 mg 500 mg

Dypracet® 20 mg/500 mg Tablets
(Dihydrocodeine Tartrate 20 mg & Paracetamol 500 mg)

112 tablets

Each tablet contains Paracetamol 500 mg and Dihydrocodeine Tartrate 20 mg.

For oral use only.

Please read the enclosed package leaflet before use.

KEEP MEDICINES OUT OF THE REACH AND SIGHT OF CHILDREN

Medicinal product subject to medical prescription.

Contains paracetamol. Immediate medical advice should be sought in the event of an overdose, even if you feel well.

Do not take with any other paracetamol containing products.

PL No. 11987/031 - PA 1385/13/1
Product Licence Holder: Auden McKenzie (Pharma Division) Ltd. Mckenzie House, Bury Street, Bury, Bury BL8 4NL, UK.

B/N XXXX
Exp xx/yyyy

20 mg 500 mg

Dypracet® 30 mg/500 mg Tablets
(Dihydrocodeine Tartrate 30 mg & Paracetamol 500 mg)

56 tablets

Each tablet contains Paracetamol 500 mg and Dihydrocodeine Tartrate 30 mg.

For oral use only.

Please read the enclosed package leaflet before use.

KEEP MEDICINES OUT OF THE REACH AND SIGHT OF CHILDREN

Medicinal product subject to medical prescription.

Contains paracetamol. Immediate medical advice should be sought in the event of an overdose, even if you feel well.

Do not take with any other paracetamol containing products.

PL No. 11967/031 - PA 1382/13/2
Product Licence Holder: Auden McKenzie (Pharma Division) Ltd. Mckenzie House, Bury Street, Bury, Bury BL8 4NL, UK.

B/N XXXX
Exp xx/yyyy

30 mg 500 mg
Module 5
Scientific discussion during initial procedure

I  INTRODUCTION
Based on the review of the data on quality, safety and efficacy, Ireland and the UK considered that the application for Dypracet 20 mg/500 mg and 30 mg/500 mg Tablets could be approved. This prescription only medicine (POM) is indicated for the treatment of severe pain.

These applications for Dypracet 20 mg/500 mg and 30 mg/500 mg Tablets were submitted according to Article 10(1) of Directive 2001/83/EC, as amended, claiming to be generic medicinal products of Remedeine and Remedeine Forte Tablets, first authorised in the UK to Napp Laboratories Limited on 20th November 1991 (PL 00337/0192-3). These licences have since undergone a change of ownership to Napp Pharmaceuticals Limited on 1st June 1999 (PL 16950/0059-60).

Paracetamol has analgesic and antipyretic actions similar to those of aspirin with weak anti-inflammatory effects. Dihydrocodeine is an analgesic with uses similar to those of morphine but has only mild sedative effects.

No new non-clinical studies were conducted, which is acceptable given that the products contain widely-used, well-known drug substances. No clinical studies, with the exception of the bioequivalence studies, have been performed and none are required for these applications as the pharmacology of dihydrocodeine hydrogen tartrate and paracetamol is well-established.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the community, the RMS has accepted copies of current GMP Certificates or satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.
II. ABOUT THE PRODUCT

| Name of the product in the Reference Member State | Dypracet 20 mg/500 mg Tablets  
Dypracet 30 mg/500 mg Tablets |
|-------------------------------------------------|---------------------------------------------------------------------------------|
| Name(s) of the drug substance(s) (INN)            | Dihydrocodeine hydrogen tartrate  
Paracetamol |
| Pharmacotherapeutic classification (ATC code)    | Natural opium alkaloids  
ATC code: N02AA. |
| Pharmaceutical form and strength(s)              | 20 mg dihydrocodeine hydrogen tartrate/500 mg paracetamol tablets  
30 mg dihydrocodeine hydrogen tartrate/500 mg paracetamol tablets |
| Reference numbers for the Decentralised Procedure | UK/H/4104/001/DC  
UK/H/4104/002/DC |
| Reference Member State                           | United Kingdom (UK) |
| Member States concerned                          | Ireland (IE) |
| Marketing Authorisation Number(s)               | PL 17507/0151  
PL 17507/0152 |
| Name and address of the authorisation holder     | Auden Mckenzie (Pharma Division) Ltd  
McKenzie House  
Bury Street  
Ruislip  
Middlesex  
HA4 7TL  
United Kingdom. |
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Drug substance

INN/Ph.Eur name: Dihydrocodeine hydrogen tartrate

Chemical name: 4,5α-Epoxy-3-methoxy-17-methylmorphinan-6α-ol hydrogen (2R,3R)-2,3-dihydroxybutanedioate

Structure:

Physical form: White or almost white crystalline powder.
Solubility: Freely soluble in water and sparingly soluble in alcohol.

Molecular formula: C_{18}H_{23}NO_{3} C_{4}H_{6}O_{6}
Molecular weight: 451.5

INN/Ph.Eur name: Paracetamol

Chemical name: N-(4-Hydroxyphenyl)acetamide

Structure:

Physical form: White or almost white crystalline powder.
Solubility: sparingly soluble in water, freely soluble in alcohol and very slightly soluble in methylene chloride.

Molecular formula: C_{8}H_{9}NO_{2}
Molecular weight: 151.2
The sources of dihydrocodeine hydrogen tartrate and paracetamol used in the product comply with their relevant European Pharmacopoeia monographs.

The manufacturers of the drug substances hold valid EDQM (European Directorate for the Quality of Medicines and Healthcare) Certificates of Suitability. The quality of the substances is suitably controlled in line with the current edition of the relevant European Pharmacopoeia Monographs.

The manufacturing process, control of materials, control of critical steps, validation and process development for dihydrocodeine hydrogen tartrate and paracetamol were assessed and approved by the EDQM in relation to the granting of the Certificates of Suitability and are therefore satisfactory.

Appropriate specifications with suitable test methods and limits are provided for the drug substances. The methods of testing and limits for residual solvents are in compliance with current guidelines. Batch analysis data are provided and comply with the proposed specifications.

The container closure system for dihydrocodeine hydrogen tartrate complies with the container closure specified on the Certificate of Suitability. The primary packaging for paracetamol has been shown to comply with current guidelines.

The re-test period for dihydrocodeine hydrogen tartrate complies with the re-test period specified on the Certificate of Suitability. Stability studies have been performed with paracetamol and no significant changes were observed. On the basis of the results, a suitable re-test period could be approved.
P. Medicinal Product

Other Ingredients
Other ingredients in the tablet core consist of pharmaceutical excipients microcrystalline cellulose, povidone K30, colloidal anhydrous silica and magnesium stearate.

All excipients comply with their respective European Pharmacopoeia monographs.

None of the excipients used contain material of animal or human origin. The magnesium stearate used is of vegetable origin.

No genetically modified organisms (GMO) have been used in the preparation of these products.

Pharmaceutical Development
The objective of the development programme was to produce safe, efficacious products containing dihydrocodeine hydrogen tartrate and paracetamol that could be considered generic medicinal products of Remedeine and Remedeine Forte Tablets.

The applicant has provided suitable product development sections. Valid justifications for the use and amounts of each excipient have been provided.

Comparative in vitro impurity and dissolution profiles have been provided for the proposed and reference products.

Manufacturing Process
Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. Process validation data on batches of each strength have been provided and are satisfactory. The applicant has committed to perform process validation on future commercial-scale batches.

Finished Product Specification
The finished product specifications are acceptable. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided for any working standards used.
Container-Closure System
These products are packaged in the following containers:
   i) High-density polyethylene (HDPE) containers with polypropylene lids.
   ii) Polyvinyl chloride (PVC) foiled aluminium blisters.

The products come in the following pack sizes:
   i) HDPE containers:
      For the 20 mg/500 mg strength: 56 and 112 tablets.
      For the 30 mg/500 mg mg strength: 56 tablets.
   ii) PVC foiled aluminium blisters:
      For the 20 mg/500 mg strength: 56 and 112 tablets
      For the 30 mg/500 mg mg strength: 56 tablets.

Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary product packaging complies with the relevant EU directives and legislation.

Stability of the product
Stability studies were performed on batches of the finished products in the packaging proposed for marketing and in accordance with current guidelines. These data support an adequate shelf-life of 24 months with no special storage instructions.

Summary of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and Labelling
The SmPCs, PIL and labelling are pharmaceutically acceptable. The UK approved SmPCs, PIL and labelling are included in modules 2, 3 and 4 of this report.

User testing results have been submitted for the PIL for this product. The results indicate that the PIL is in accordance with Article 59 of Council Directive 2001/83/EC, as amended and is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

MAA Forms
The MAA forms are pharmaceutically satisfactory.

Quality Ovaaall Summary
The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion
From a quality point of view, it is recommended that Marketing Authorisations are granted for these applications.
III.2 NON-CLINICAL ASPECTS

The pharmacodynamics, pharmacokinetics and toxicological properties of dihydrocodeine hydrogen tartrate and paracetamol are well-known. As dihydrocodeine hydrogen tartrate and paracetamol are widely used, well-known drug substances, the applicant has not provided any new non-clinical data and none are required. An overview based on literature is therefore appropriate.

Non-Clinical Overview
The non-clinical overview has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

Impurities
The impurities identified in the drug substances and drug product have satisfactory proposed limits which all comply with current international conference on harmonisation of technical requirements for registration of pharmaceuticals for human use (ICH) guidelines.

Environmental Risk Assessment
A satisfactory justification has been provided for the absence of an Environmental Risk Assessment.

Conclusion
From a non-clinical point of view, it is recommended that Marketing Authorisations are granted for these applications.
III.3 CLINICAL ASPECTS
Clinical Pharmacology

With the exception of the following bioequivalence studies, no new pharmacokinetic or pharmacodynamic data were submitted with these applications and none were required.

Pharmacokinetics

Bioequivalence study 1

A two-period, two-sequence, single-dose, crossover study to compare the pharmacokinetics of the test product Dypracet 20 mg/500 mg Tablets versus the reference product Remedeine (20 mg dihydrocodeine hydrogen tartrate/500 mg paracetamol) Tablets (Napp Pharmaceuticals Limited) healthy subjects under fasted conditions.

Blood samples were taken pre- and up to 24 hours post dose. The washout period between each treatment period was one week. Pharmacokinetic parameters were measured from the plasma and statistically analysed.

Results for dihydrocodeine hydrogen tartrate and paracetamol are presented below as log-transformed values for geometric means:

Dihydrocodeine hydrogen tartrate

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC_{0-t} (ng.h/mL)</th>
<th>AUC_{0-∞} (ng.h/mL)</th>
<th>C_{max} (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test (T)</td>
<td>579.87</td>
<td>609.91</td>
<td>125.39</td>
</tr>
<tr>
<td>Reference (R)</td>
<td>590.28</td>
<td>624.45</td>
<td>126.43</td>
</tr>
<tr>
<td>T/R Ratio (90% CI)</td>
<td>98.24 (93.29 – 103.45)</td>
<td>97.67 (92.90 – 102.69)</td>
<td>99.18 (90.35 – 108.87)</td>
</tr>
</tbody>
</table>

AUC_{0-t} area under the plasma concentration-time curve from time zero to infinity
AUC_{0-∞} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration

Paracetamol

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC_{0-t} (ng.h/mL)</th>
<th>AUC_{0-∞} (ng.h/mL)</th>
<th>C_{max} (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test (T)</td>
<td>23318.29</td>
<td>25756.28</td>
<td>9382.88</td>
</tr>
<tr>
<td>Reference (R)</td>
<td>23167.10</td>
<td>26177.44</td>
<td>9504.16</td>
</tr>
<tr>
<td>T/R Ratio (90% CI)</td>
<td>100.65 (95.92 – 103.45)</td>
<td>98.39 (94.23 – 102.74)</td>
<td>98.72 (86.54 – 112.62)</td>
</tr>
</tbody>
</table>

The results for the primary variables indicated that the 90% confidence intervals test/reference ratio of geometric means for AUC_{0-t} and C_{max} for dihydrocodeine hydrogen tartrate and paracetamol lie within acceptance criteria of 80.00-125.00%. Thus, bioequivalence has been shown between the test and reference products in this study.
Bioequivalence study 2

A two-period, two-sequence, single-dose, crossover study to compare the pharmacokinetics of the test product Dypracet 30 mg/500 mg Tablets versus the reference product Remedeine Forte (30 mg dihydrocodeine hydrogen tartrate/500 mg paracetamol) Tablets (Napp Pharmaceuticals Limited) healthy subjects under fasted conditions.

Blood samples were taken pre- and up to 24 hours post dose. The washout period between each treatment period was one week. Pharmacokinetic parameters were measured from the plasma and statistically analysed.

Results for dihydrocodeine hydrogen tartrate and paracetamol are presented below as log-transformed values for geometric means:

### Dihydrocodeine hydrogen tartrate

<table>
<thead>
<tr>
<th>Treatment</th>
<th>( \text{AUC}_{0-t} ) (ng.h/mL)</th>
<th>( \text{AUC}_{0-\infty} ) (ng.h/mL)</th>
<th>( \text{C}_{\text{max}} ) (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test (T)</td>
<td>946.91</td>
<td>981.79</td>
<td>158.11</td>
</tr>
<tr>
<td>Reference (R)</td>
<td>984.24</td>
<td>1017.23</td>
<td>161.19</td>
</tr>
<tr>
<td><strong>T/R Ratio</strong></td>
<td><strong>96.21</strong></td>
<td><strong>96.52</strong></td>
<td><strong>98.09</strong></td>
</tr>
<tr>
<td>(90% CI)</td>
<td>(93.13 – 99.39)</td>
<td>(93.94 – 99.64)</td>
<td>(91.84 – 104.77)</td>
</tr>
</tbody>
</table>

### Paracetamol

<table>
<thead>
<tr>
<th>Treatment</th>
<th>( \text{AUC}_{0-t} ) (ng.h/mL)</th>
<th>( \text{AUC}_{0-\infty} ) (ng.h/mL)</th>
<th>( \text{C}_{\text{max}} ) (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test (T)</td>
<td>19203.02</td>
<td>22059.90</td>
<td>6700.94</td>
</tr>
<tr>
<td>Reference (R)</td>
<td>19728.68</td>
<td>22184.23</td>
<td>6837.79</td>
</tr>
<tr>
<td><strong>T/R Ratio</strong></td>
<td><strong>97.34</strong></td>
<td><strong>99.44</strong></td>
<td><strong>98.00</strong></td>
</tr>
<tr>
<td>(90% CI)</td>
<td>(92.24 – 102.71)</td>
<td>(94.92 – 104.16)</td>
<td>(88.21 – 108.87)</td>
</tr>
</tbody>
</table>

The results for the primary variables indicated that the 90% confidence intervals test/reference ratio of geometric means for \( \text{AUC}_{0-t} \) and \( \text{C}_{\text{max}} \) for dihydrocodeine hydrogen tartrate and paracetamol lie within acceptance criteria of 80.00-125.00%. Thus, bioequivalence has been shown between the test and reference products in this study.

The bioequivalence study data provided demonstrate that Dypracet 20 mg/500 mg and 30 mg/500 mg Tablets are equivalent to, and therefore generic products of the reference products, Remedeine and Remedeine Forte Tablets.

**Efficacy**
No new efficacy data were submitted with these generic applications and none were required.

**Safety**
With the exception of the data submitted during the bioequivalence studies, no new safety data were submitted with these generic applications and none were required. No new or unexpected safety concerns were raised during the bioequivalence studies.
The Pharmacovigilance System and Risk Management Plan
The RMS considers that the pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

A satisfactory justification has been provided for the absence of a Risk Management Plan.

Summary of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and Labelling
The SmPCs, PIL and labelling are clinically satisfactory and consistent with those for the reference products, where appropriate.

Clinical Overview
The clinical overview has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

MAA Forms
The MAA forms are clinically satisfactory.

Conclusions
From a clinical point of view, it is recommended that Marketing Authorisations are granted for these applications.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT
QUALITY
The important quality characteristics of Dypracet 20 mg/500 mg and 30 mg/500 mg Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit-risk balance.

NON-CLINICAL
No new non-clinical data were submitted and none are required for applications of this type.

CLINICAL
Bioequivalence has been demonstrated between Dypracet 20 mg/500 mg and 30 mg/500 mg Tablets and the reference products, Remedeine and Remedeine Forte Tablets.

No new or unexpected safety concerns arose from the bioequivalence studies.

The SmPCs, PIL and labelling are satisfactory and consistent with those for the reference products.

BENEFIT-RISK ASSESSMENT
The quality of the products is acceptable and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with dihydrocodeine hydrogen tartrate and paracetamol is considered to have demonstrated the therapeutic value of the compounds. The benefit-risk ratio is, therefore, considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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