

## **Public Assessment Report**

**Mypaid 60mg SR Tablets  
Mypaid 90mg SR Tablets  
Mypaid 120mg SR Tablets**

**Sandoz**

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## Lay Summary

The MHRA granted Marketing Authorisations (licenses) for Mypaid 60mg, 90mg and 120mg SR Tablets on the 2<sup>nd</sup> May 2006. These products are prescription only medicines.

Mypaid tablets contain dihydrocodeine tartrate, an opioid analgesic used for the treatment of severe pain in cancer and other chronic conditions. Mypaid SR Tablets have been formulated to provide a prolonged release of the active ingredient.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Mypaid 60mg, 90mg, and 120mg SR Tablets outweigh the risks, hence Marketing Authorisations have been granted.

## SCIENTIFIC DISCUSSION

### Introduction

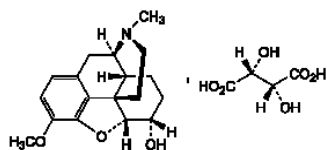
The MHRA granted marketing authorisations for the medicinal products Mypaid 60mg, 90mg and 120mg SR Tablets (PL 04416/0580-2) on 2<sup>nd</sup> May 2006. These applications successfully claimed that the products were generic medical products of DHC Continus Tablets 60mg (PL 16950/0019), 90mg (PL 16950/0020) and 120mg (PL 16950/0021), marketed by Napp Pharmaceuticals and granted 12 July 1990. The legal basis of the application was EU Directive 2001/83/EC Article 10.1.

The active ingredient in Mypaid SR Tablets is dihydrocodeine tartrate, a semisynthetic opioid analgesic (ATC code NO2A AO8). The formulation of Mypaid SR Tablets is designed to give a prolonged release of the active ingredient.

## PHARMACEUTICAL ASSESSMENT

### Active Substance

The active substance is Dihydrocodeine tartrate



Structure:

Description: White or almost white crystalline powder

Molecular formula:  $C_{22}H_{29}NO_9$

Relative molecular mass: 451.46

Dihydrocodeine is covered by a European Drug Master File and a letter of access was provided. The impurities are controlled by the levels in the European Pharmacopoeia monograph and the DMF. The specification and analytical methods used by the active substance manufacturer is that in the European Pharmacopoeia as supplemented by the DMF. Satisfactory batch data from three batches were provided. Certificates of analysis have been provided by the active substance manufacturer for the dihydrocodeine hydrogen tartrate and related substances which were used as reference standards. The active ingredient is stored in containers which meet EC standards. The retest period for the active ingredient is two years and this was supported by satisfactory stability data.

## Finished Product

The tablets are round, flat and white to off white in colour. The tablets are packed in blisters PVC/PVDC and sealed with aluminium foil with printing. The qualitative composition of Mypaid SR Tablets is given below. The manufacturer declared that there are no excipients of animal or human origin in the product.

Dihydrocodeine hydrogen tartrate
Glyceryl behenate
Calcium sulphate dihydrate
Copovidone VA 64
Sodium stearyl fumarate
Purified water

The aim was to develop three oral dosages in the form of a prolonged release preparation, similar to the reference products.

Bioequivalence trials carried out on the drug products were compared to the corresponding strength of the reference product DHC Continus tablets. Comparative dissolution and impurity profiles were carried out under identical conditions and are found to be similar for both the reference and test product.

A satisfactory description of the manufacturing process and in-process controls and satisfactory validation data from three batches was provided. An acceptable Finished Product Specification, Certificates of Analysis and details of analytical methods was also provided.

The tablets are packed in PVC/PVDC rigid film non transparent blisters and covered by aluminium foil. Specifications certificates of analysis are provided. Stability data supports the shelf-life of 24 months.

## Conclusion

A marketing authorisation was granted.

**PRECLINICAL ASSESSMENT**

No preclinical data were submitted for this application and none were required.

## CLINICAL ASSESSMENT

### CLINICAL PHARMACOLOGY

Dihydrocodeine is a semisynthetic narcotic analgesic with a potency between morphine and codeine. It acts on opioid receptors in the brain to reduce the patient's perception of pain and improve the psychological reaction to pain by reducing the associated anxiety.

Dihydrocodeine is well absorbed from the gastrointestinal tract following administration and plasma levels are maintained throughout the twelve hour dosing interval.

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 o-demethylation, n-demethylation and 6-keto reduction.

### EFFICACY

Efficacy was reviewed in the Clinical Expert Report. The reference product is established and the application depends upon the ability to show bioequivalence with the reference product.

### SAFETY

Safety was reviewed in the Clinical Expert Report. The reference product is established and the application depends upon the ability to show bioequivalence with the reference product.

### BIOEQUIVALENCE

Bioequivalence has been demonstrated in a single dose fasted study on a 120mg modified release strength, a single dose food effect study on a 120mg modified release strength and a multiple dose on a 60mg modified release strength.

#### Single-dose in fasted state

38 healthy volunteers of both genders were phenotyped and 26 volunteers were included in the bioequivalence study, 25 participants completed the whole study.

#### Primary pharmacokinetic parameters

Pharmacokinetic parameter	test product	reference product	point estimate
AUC <sub>0-inf</sub>	2162.98 ng.hrs/ml	2151.13 ng.hrs/ml	1.010
C <sub>max</sub>	199.56 ng/ml	198.60 ng/ml	1.000
AUC <sub>0-t</sub>	2094.79 ng.hrs/ml	2082.38 ng.hrs/ml	1.010

Bioequivalence of two dihydrocodeine formulations after a single oral dose was analysed. The statistical analysis was done by means of inclusions of the 90% confidence limits for the pharmacokinetic parameters AUC<sub>0-t</sub>, AUC<sub>0-inf</sub> and C<sub>max</sub> in required range of 0.80-1.25.

Pharmacokinetic parameters for DHC 120 SR Tablets (Slovakofarma, a.s.) were within the bioequivalence range 80-125% both AUC and C<sub>max</sub>.

**Single-dose with food ingestion (120mg)**

Healthy volunteers were phenotyped by dextromethorphan. 30 volunteers were included in bioequivalence testing: 26 participants completed the whole study.

**Primary pharmacokinetic parameters**

Pharmacokinetic parameter	test product	reference product	point estimate
AUC <sub>0-inf</sub>	2118.42 ng.hrs/ml	2137.22 ng.hrs/ml	0.992
C <sub>max</sub>	214.61 ng/ml	213.62 ng/ml	1.004
AUC <sub>0-t</sub>	2063.34 ng.hrs/ml	2077.86 ng.hrs/ml	0.994

ANOVA performed on the pharmacokinetic indices did not detect any significant differences between the two formulations for any of the parameters AUC<sub>0-t</sub>, AUC<sub>0-inf</sub> and C<sub>max</sub>.

Pharmacokinetic parameters for DHC 120 SR Tablets (Slovakofarma, a.s.) were within the bioequivalence range 80-125% both AUC and C<sub>max</sub>.

**Multiple dose (60mg)**

32 healthy volunteers were phenotyped, 26 were included and 24 participants completed the bioequivalence study.

**Primary pharmacokinetic parameters**

Pharmacokinetic parameter	test product	reference product	point estimate
AUC <sub>t</sub>	902.12 ng.hrs/ml	896.92 ng.hrs/ml	0.999
C <sub>max</sub>	125.81 ng/ml	124.91 ng/ml	1.007

Pharmacokinetic parameters for DHC 120 SR Tablets (Slovakofarma, a.s.) were within the bioequivalence range 80-125% both AUC and C<sub>max</sub>.

**EXPERT REPORT**

The expert report is written by a medically qualified pharmaceutical consultant and is satisfactory.

**SUMMARY OF PRODUCT CHARACTERISTICS**

This was satisfactory

**Clinical Conclusion**

The applicant has demonstrated that Mypaid SR Tablets are bioequivalent to the reference product. A marketing authorisation was granted.

## **OVERALL CONCLUSION AND RISK/BENEFIT ANALYSIS**

### **QUALITY**

The important quality characteristics of Mypaid SR 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.

### **PRECLINICAL**

No new preclinical data were submitted and none are required for applications of this type.

### **EFFICACY**

Bioequivalence has been demonstrated between the applicant's Mypaid SR Tablets and DHC Continus Tablets.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with that for tablets.

### **RISK BENEFIT ASSESSMENT**

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant's products and the innovator products are interchangeable. The risk benefit is, therefore, considered to be positive.



**STEPS TAKEN DURING ASSESSMENT**

1	The MHRA received the application on 22 <sup>nd</sup> December 2004.
2	Pre-assessment checks were completed on 10 <sup>th</sup> February 2005.
3	The Clinical Assessment was begun on 15 <sup>th</sup> March 2006 and was completed on 23 <sup>rd</sup> March 2006.
4	The Quality Assessment was begun on 7 <sup>th</sup> November 2005, further information was requested on 18 <sup>th</sup> November 2005 and a response was received on 24 <sup>th</sup> March 2006.
5	A Marketing Authorisation was granted on 2 <sup>nd</sup> May 2006.

**Steps Taken After Assessment**

None

## SUMMARY OF PRODUCT CHARACTERISTICS

### 1. NAME OF THE MEDICINAL PRODUCT

Mypaid 60mg SR Tablets.

### 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 60mg dihydrocodeine tartrate.

For excipients, see section 6.1.

### 3. PHARMACEUTICAL FORM

Prolonged-release tablets.

Round, flat, white to off-white tablets.

## 4. CLINICAL PARTICULARS

### 4.1. Therapeutic indications

For the relief of severe pain in cancer and other chronic conditions.

### 4.2. Posology and method of administration

Oral

The tablets should not be chewed.

*Adults and children older than 12 years:* 60 mg - 120 mg every 12 hours.

*Elderly:* Dosage should be reduced.

*Children up to 12 years:* Not recommended.

### 4.3. Contraindications

Hypersensitivity to dihydrocodeine or any of the excipients.

Respiratory depression, obstructive airways disease.

As dihydrocodeine may cause the release of histamine, it should not be given during an asthma attack.

Avoid in acute alcoholism and where there is a risk of paralytic ileus.

Opioid analgesics should not be administered to patients with increased intracranial pressure and head injury.

Avoid concomitant use with and for 2 weeks after stopping MAOIs

### 4.4. Special warnings and precautions for use

Caution should be exercised in hypotension, hypothyroidism, asthma (see 4.3), decreased respiratory reserve, prostatic hypertrophy and convulsive disorders. Severe withdrawal symptoms may occur in dependent patients if treatment is withdrawn abruptly.

The dose should be reduced in elderly and debilitated patients. Reduce dose or avoid in hepatic or renal function impairment.

### 4.5. Interactions with other medicinal products and other forms of interaction

Opioid analgesics may interact with the following:

Alcohol - enhanced hypotensive and sedative effects

Antidepressants, Tricyclic - sedative effects possibly increased

Antipsychotics - enhanced hypotensive and sedative effects

Anxiolytics and Hypnotics - increased sedative effect

Cimetidine - metabolism of opioid analgesics inhibited by cimetidine (increased plasma concentration)

Ciprofloxacin - avoid premedication with opioid analgesics (reduced plasma concentration of ciprofloxacin) when ciprofloxacin used for surgical prophylaxis.

Domperidone - opioid analgesics antagonise effects of domperidone on gastrointestinal activity

MAOIs - possible CNS excitation or depression (hypertension or hypotension) when opioid analgesics given with MAOIs —avoid concomitant use and for 2 weeks after stopping MAOIs

Metoclopramide - opioid analgesics antagonise effects of metoclopramide on gastro-intestinal activity.

Mexiletine - opioid analgesics delay absorption of mexiletine

Moclobemide - possible CNS excitation or depression (hypertension or hypotension)

*Ritonavir* - plasma concentration of opioid analgesics (except methadone) possibly increased by ritonavir

There is an increased risk of toxicity with myelosuppressive drugs

#### **4.6. Pregnancy and lactation**

Dihydrocodeine has been taken in pregnancy, although there is very little published about its safety.

*Third trimester:* Depression of neonatal respiration; withdrawal effects in neonates of dependent mothers; gastric stasis and risk of inhalation pneumonia in mother during labour.

Dihydrocodeine has not been reported to be excreted in breast milk. However, it is advisable that dihydrocodeine only be administered to breast-feeding mothers if considered essential.

#### **4.7. Effects on ability to drive and use machines**

Dihydrocodeine may cause drowsiness: If affected, patients should not drive or operate machinery.

#### **4.8. Undesirable effects**

Nausea and vomiting (particularly in initial stages), constipation, and drowsiness; larger doses may produce respiratory depression and hypotension. Other side-effects include abdominal pain, difficulty with micturition, urinary retention, ureteric or biliary spasm, dry mouth, sweating, paraesthesia, headache, facial flushing, vertigo, bradycardia, tachycardia, palpitations, postural hypotension, hypothermia, confusion, hallucinations, dysphoria, mood changes, dependence, miosis, decreased libido or potency, rashes, urticaria and pruritus.

#### 4.9. Overdose

Opioid analgesics cause varying degrees of coma, respiratory depression, and pinpoint pupils. The specific antidote naloxone is indicated if there is coma or bradypnoea.

Since naloxone has a shorter duration of action than many opioids, close monitoring and repeated injections are necessary according to the respiratory rate and depth of coma. Where repeated administration of naloxone is required, it may be given by continuous intravenous infusion and the rate of infusion adjusted according to vital signs.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1. Pharmacodynamic properties

*Pharmacotherapeutic Group:* Analgesics, Natural Opium Alkaloids – Dihydrocodeine

*ATC code:* NO2A AO8

Dihydrocodeine is a semisynthetic narcotic analgesic with a potency between morphine and codeine. It acts on opioid receptors in the brain to reduce the patient's perception of pain and improve the psychological reaction to pain by reducing the associated anxiety.

### 5.2. Pharmacokinetic properties

Dihydrocodeine is well absorbed from the gastrointestinal tract following administration and plasma levels are maintained throughout the twelve hour dosing interval.

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 o-demethylation, n-demethylation and 6-keto reduction.

**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**

Glyceryl behenate  
Calcium sulphate dihydrate  
Copovidone VA 64  
Sodium stearyl fumarate

**6.2. Incompatibilities**

Not applicable

**6.3. Shelf life**

3 years

**6.4. Special precautions for storage**

Store below 25°C

**6.5. Nature and contents of container**

PVC/PVDC/Aluminium foil blister  
Packs containing 56 or 60 tablets. Not all pack sizes may be marketed.

**6.6. Instruction for use and handling**

Not applicable

**7. MARKETING AUTHORISATION HOLDER**

Sandoz Ltd  
37 Woolmer Way  
Bordon  
Hampshire  
GU35 9QE

**8. MARKETING AUTHORISATION NUMBER**

PL 04416/0580

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

02/05/2006

**10 DATE OF REVISION OF THE TEXT**

02/05/2006



## **SUMMARY OF PRODUCT CHARACTERISTICS**

### **1. NAME OF THE MEDICINAL PRODUCT**

Mypaid 90mg SR Tablets.

### **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each tablet contains 90mg dihydrocodeine tartrate.

For excipients, see section 6.1.

### **3. PHARMACEUTICAL FORM**

Prolonged-release tablets.

Round, flat, white to off-white tablets.

## **4. CLINICAL PARTICULARS**

### **4.1. Therapeutic indications**

For the relief of severe pain in cancer and other chronic conditions.

### **4.2. Posology and method of administration**

Oral

The tablets should not be chewed.

*Adults and children older than 12 years:* 60 mg - 120 mg every 12 hours.

*Elderly:* Dosage should be reduced.

*Children up to 12 years:* Not recommended.

### 4.3. Contraindications

Hypersensitivity to dihydrocodeine or any of the excipients.

Respiratory depression, obstructive airways disease.

As dihydrocodeine may cause the release of histamine, it should not be given during an asthma attack.

Avoid in acute alcoholism and where there is a risk of paralytic ileus.

Opioid analgesics should not be administered to patients with increased intracranial pressure and head injury.

Avoid concomitant use with and for 2 weeks after stopping MAOIs

### 4.4. Special warnings and precautions for use

Caution should be exercised in hypotension, hypothyroidism, asthma (see 4.3), decreased respiratory reserve, prostatic hypertrophy and convulsive disorders. Severe withdrawal symptoms may occur in dependent patients if treatment is withdrawn abruptly.

The dose should be reduced in elderly and debilitated patients. Reduce dose or avoid in hepatic or renal function impairment.

### 4.5. Interactions with other medicinal products and other forms of interaction

Opioid analgesics may interact with the following:

Alcohol - enhanced hypotensive and sedative effects

Antidepressants, Tricyclic - sedative effects possibly increased

Antipsychotics - enhanced hypotensive and sedative effects

Anxiolytics and Hypnotics - increased sedative effect

Cimetidine - metabolism of opioid analgesics inhibited by cimetidine (increased plasma concentration)

Ciprofloxacin - avoid premedication with opioid analgesics (reduced plasma concentration of ciprofloxacin) when ciprofloxacin used for surgical prophylaxis.

Domperidone - opioid analgesics antagonise effects of domperidone on gastrointestinal activity

MAOIs - possible CNS excitation or depression (hypertension or hypotension) when opioid analgesics given with MAOIs —avoid concomitant use and for 2 weeks after stopping MAOIs

Metoclopramide - opioid analgesics antagonise effects of metoclopramide on gastro-intestinal activity.

Mexiletine - opioid analgesics delay absorption of mexiletine

Moclobemide - possible CNS excitation or depression (hypertension or hypotension)

Ritonavir - plasma concentration of opioid analgesics (except methadone) possibly increased by ritonavir

There is an increased risk of toxicity with myelosuppressive drugs

#### **4.6. Pregnancy and lactation**

Dihydrocodeine has been taken in pregnancy, although there is very little published about its safety.

*Third trimester:* Depression of neonatal respiration; withdrawal effects in neonates of dependent mothers; gastric stasis and risk of inhalation pneumonia in mother during labour.

Dihydrocodeine has not been reported to be excreted in breast milk. However, it is advisable that dihydrocodeine only be administered to breast-feeding mothers if considered essential.

#### **4.7. Effects on ability to drive and use machines**

Dihydrocodeine may cause drowsiness: If affected, patients should not drive or operate machinery.

#### **4.8. Undesirable effects**

Nausea and vomiting (particularly in initial stages), constipation, and drowsiness; larger doses may produce respiratory depression and hypotension. Other side-effects include abdominal pain, difficulty with micturition, urinary retention, ureteric or biliary spasm, dry mouth, sweating, paraesthesia, headache, facial flushing, vertigo, bradycardia, tachycardia, palpitations, postural hypotension, hypothermia, confusion, hallucinations, dysphoria, mood changes, dependence, miosis, decreased libido or potency, rashes, urticaria and pruritus.

#### **4.9. Overdose**

Opioid analgesics cause varying degrees of coma, respiratory depression, and pinpoint pupils. The specific antidote naloxone is indicated if there is coma or bradypnoea.

Since naloxone has a shorter duration of action than many opioids, close monitoring and repeated injections are necessary according to the respiratory rate and depth of coma. Where repeated administration of naloxone is required, it may be given by continuous intravenous infusion and the rate of infusion adjusted according to vital signs.

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1. Pharmacodynamic properties**

*Pharmacotherapeutic Group:* Analgesics, Natural Opium Alkaloids – Dihydrocodeine

*ATC code:* NO2A AO8

Dihydrocodeine is a semisynthetic narcotic analgesic with a potency between morphine and codeine. It acts on opioid receptors in the brain to reduce the patient's perception of pain and improve the psychological reaction to pain by reducing the associated anxiety.

### **5.2. Pharmacokinetic properties**

Dihydrocodeine is well absorbed from the gastrointestinal tract following administration and plasma levels are maintained throughout the twelve hour dosing interval.

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 o-demethylation, n-demethylation and 6-keto reduction.

**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**

Glyceryl behenate  
Calcium sulphate dihydrate  
Copovidone VA 64  
Sodium stearyl fumarate

**6.2. Incompatibilities**

Not applicable

**6.3. Shelf life**

3 years

**6.4. Special precautions for storage**

Store below 25°C

**6.5. Nature and contents of container**

PVC/PVDC/Aluminium foil blister  
Packs containing 56 or 60 tablets. Not all pack sizes may be marketed.

**6.6. Instruction for use and handling**

Not applicable

**7. MARKETING AUTHORISATION HOLDER**

Sandoz Ltd  
37 Woolmer Way  
Bordon  
Hampshire  
GU35 9QE

**8. MARKETING AUTHORISATION NUMBER**

PL 04416/0581

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

02/05/2006

**10. DATE OF REVISION OF THE TEXT**

02/05/2006

## **SUMMARY OF PRODUCT CHARACTERISTICS**

### **1. NAME OF THE MEDICINAL PRODUCT**

Mypaid 120mg SR Tablets.

### **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each tablet contains 120mg dihydrocodeine tartrate.

For excipients, see section 6.1.

### **3. PHARMACEUTICAL FORM**

Prolonged-release tablets.

Round, flat, white to off-white tablets, half scored on one side.

## **4. CLINICAL PARTICULARS**

### **4.1. Therapeutic indications**

For the relief of severe pain in cancer and other chronic conditions.

### **4.2. Posology and method of administration**

Oral

The tablets should not be chewed.

*Adults and children older than 12 years:* 60 mg - 120 mg every 12 hours.

*Elderly:* Dosage should be reduced.

*Children up to 12 years:* Not recommended.

### 4.3. Contraindications

Hypersensitivity to dihydrocodeine or any of the excipients.

Respiratory depression, obstructive airways disease.

As dihydrocodeine may cause the release of histamine, it should not be given during an asthma attack.

Avoid in acute alcoholism and where there is a risk of paralytic ileus.

Opioid analgesics should not be administered to patients with increased intracranial pressure and head injury.

Avoid concomitant use with and for 2 weeks after stopping MAOIs

### 4.4. Special warnings and precautions for use

Caution should be exercised in hypotension, hypothyroidism, asthma (see 4.3), decreased respiratory reserve, prostatic hypertrophy and convulsive disorders. Severe withdrawal symptoms may occur in dependent patients if treatment is withdrawn abruptly.

The dose should be reduced in elderly and debilitated patients. Reduce dose or avoid in hepatic or renal function impairment.

### 4.5. Interactions with other medicinal products and other forms of interaction

Opioid analgesics may interact with the following:

Alcohol - enhanced hypotensive and sedative effects

Antidepressants, Tricyclic - sedative effects possibly increased

Antipsychotics - enhanced hypotensive and sedative effects

Anxiolytics and Hypnotics - increased sedative effect

Cimetidine - metabolism of opioid analgesics inhibited by cimetidine (increased plasma concentration)

Ciprofloxacin - avoid premedication with opioid analgesics (reduced plasma concentration of ciprofloxacin) when ciprofloxacin used for surgical prophylaxis.

Domperidone - opioid analgesics antagonise effects of domperidone on gastrointestinal activity

MAOIs - possible CNS excitation or depression (hypertension or hypotension) when opioid analgesics given with MAOIs —avoid concomitant use and for 2 weeks after stopping MAOIs

Metoclopramide - opioid analgesics antagonise effects of metoclopramide on gastro-intestinal activity.

Mexiletine - opioid analgesics delay absorption of mexiletine

Moclobemide - possible CNS excitation or depression (hypertension or hypotension)



*Ritonavir* - plasma concentration of opioid analgesics (except methadone) possibly increased by ritonavir

There is an increased risk of toxicity with myelosuppressive drugs

#### **4.6. Pregnancy and lactation**

Dihydrocodeine has been taken in pregnancy, although there is very little published about its safety.

*Third trimester:* Depression of neonatal respiration; withdrawal effects in neonates of dependent mothers; gastric stasis and risk of inhalation pneumonia in mother during labour.

Dihydrocodeine has not been reported to be excreted in breast milk. However, it is advisable that dihydrocodeine only be administered to breast-feeding mothers if considered essential.

#### **4.7. Effects on ability to drive and use machines**

Dihydrocodeine may cause drowsiness: If affected, patients should not drive or operate machinery.

#### **4.8. Undesirable effects**

Nausea and vomiting (particularly in initial stages), constipation, and drowsiness; larger doses may produce respiratory depression and hypotension. Other side-effects include abdominal pain, difficulty with micturition, urinary retention, ureteric or biliary spasm, dry mouth, sweating, paraesthesia, headache, facial flushing, vertigo, bradycardia, tachycardia, palpitations, postural hypotension, hypothermia, confusion, hallucinations, dysphoria, mood changes, dependence, miosis, decreased libido or potency, rashes, urticaria and pruritus.

#### **4.9. Overdose**

Opioid analgesics cause varying degrees of coma, respiratory depression, and pinpoint pupils. The specific antidote naloxone is indicated if there is coma or bradypnoea.

Since naloxone has a shorter duration of action than many opioids, close monitoring and repeated injections are necessary according to the respiratory rate and depth of coma. Where repeated administration of naloxone is required, it may be given by continuous intravenous infusion and the rate of infusion adjusted according to vital signs.

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1. Pharmacodynamic properties**

*Pharmacotherapeutic Group:* Analgesics, Natural Opium Alkaloids – Dihydrocodeine

*ATC code:* NO2A AO8

Dihydrocodeine is a semisynthetic narcotic analgesic with a potency between morphine and codeine. It acts on opioid receptors in the brain to reduce the patient's perception of pain and improve the psychological reaction to pain by reducing the associated anxiety.

### **5.2. Pharmacokinetic properties**

Dihydrocodeine is well absorbed from the gastrointestinal tract following administration and plasma levels are maintained throughout the twelve hour dosing interval.

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 o-demethylation, n-demethylation and 6-keto reduction.

**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**

Glyceryl behenate  
Calcium sulphate dihydrate  
Copovidone VA 64  
Sodium stearyl fumarate

**6.2. Incompatibilities**

Not applicable

**6.3. Shelf life**

3 years

**6.4. Special precautions for storage**

Store below 25°C

**6.5. Nature and contents of container**

PVC/PVDC/Aluminium foil blister  
Packs containing 56 or 60 tablets. Not all pack sizes may be marketed.

**6.6. Instruction for use and handling**

Not applicable

**7. MARKETING AUTHORISATION HOLDER**

Sandoz Ltd  
37 Woolmer Way  
Bordon  
Hampshire  
GU35 9QE

**8. MARKETING AUTHORISATION NUMBER**

PL 04416/0582


**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

02/05/2006

**10. DATE OF REVISION OF THE TEXT**

02/05/2006

**Labels and Leaflet**

 <b>SANDOZ</b>	<b>PATIENT INFORMATION LEAFLET</b>	SZ00000LT000
<b>Mypaid 60mg, 90mg &amp; 120mg SR Tablets (dihydrocodeine tartrate)</b>		
<p><b>Please read this leaflet carefully before you start taking this medicine.</b> Keep this leaflet. You may need to read it again. If you have further questions, please ask your doctor or your pharmacist. This medicine has been prescribed for you personally, you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.</p>		
<b>In this leaflet:</b>		
<ol style="list-style-type: none"> <li>1. <b>What Mypaid Tablets are and what they are used for.</b></li> <li>2. <b>Before you take Mypaid Tablets.</b></li> <li>3. <b>How to take Mypaid Tablets.</b></li> <li>4. <b>Possible side effects.</b></li> <li>5. <b>Storing Mypaid Tablets.</b></li> </ol>		
<p>The name of your medicine is Mypaid 60mg, 90mg or 120mg SR Tablets. Each tablet contains 60mg, 90mg or 120mg of the active substance dihydrocodeine tartrate. The other ingredients are glyceryl behenate, calcium sulphate dihydrate, copovidone VA 64 and sodium stearyl fumarate. The Marketing Authorisation Holder and Manufacturer of this medicine is Sandoz Ltd, 37 Woolmer Way, Bordon, Hampshire, GU35 9QE.</p>		
<b>1. WHAT MYPaid TABLETS ARE AND WHAT THEY ARE USED FOR.</b>		
<p>Dihydrocodeine is the active substance in Mypaid Tablets. It is an analgesic (painkiller) and is used to treat severe pain. Mypaid Tablets are prolonged-release tablets. They gradually release the dihydrocodeine during the day. This means you only need to take a tablet every 12 hours. Mypaid 60mg SR Tablets are round, flat, white to off white tablets engraved with M 60 and are available in blister packs containing 56 or 60 tablets*. Mypaid 90mg SR Tablets are round, flat, white to off white tablets engraved with M 90 and are available in blister packs containing 56 or 60 tablets*. Mypaid 120mg SR Tablets are round, flat, white to off white tablets with a score line on one side and engraved with M 120 on the other and are available in blister packs containing 56 or 60 tablets*. Your pharmacist will have dispensed the number of tablets that your doctor prescribed for you.</p>		
<b>2. BEFORE YOU TAKE MYPaid TABLETS.</b>		
<b>Do not take Mypaid Tablets:</b>		
<ul style="list-style-type: none"> <li>• If you are hypersensitive (allergic) to dihydrocodeine or any of the other ingredients that are in Mypaid tablets (see list above).</li> <li>• If you have problems breathing as a result of respiratory depression or obstructive airways disease.</li> <li>• If you are having an asthma attack.</li> <li>• If you are drunk or have acute alcoholism.</li> <li>• If you have or your doctor believes you may have an obstruction of your intestines (paralytic ileus).</li> <li>• If you have a head injury or increased pressure within your head (raised intracranial pressure).</li> <li>• If you are taking a monoamine oxidase inhibitor (MAOI) or have stopped taking one within the last two weeks.</li> </ul>		
<b>Talk to your doctor or pharmacist before taking Mypaid Tablets:</b>		
<ul style="list-style-type: none"> <li>• If you have low blood pressure.</li> <li>• If you have an under active thyroid gland (hypothyroidism).</li> <li>• If you have asthma or any problems breathing.</li> <li>• If you have an enlarged prostate gland, need to pass water frequently or have difficulty passing water.</li> <li>• If you have epilepsy or any convulsive disorder.</li> <li>• If you are elderly, frail or debilitated in any way.</li> <li>• If you have any problems with your liver or your kidneys.</li> </ul>		
<p>If any of the above applies to you, this medicine may not be suitable for you or your doctor may need to reduce the dose or strength of your tablets.</p>		
<b>Taking Mypaid Tablets with food and drink:</b>		
<p>It does not matter whether you take these tablets with food or on an empty stomach. You should avoid alcohol while taking Mypaid Tablets.</p>		
<b>Pregnancy:</b>		
<p>Dihydrocodeine has been taken in pregnancy although there is very little published about its safety. If taken in the last three months of pregnancy (third trimester) it may affect a baby's breathing. In mothers who have been taking this medicine for a long time the baby may be born with withdrawal symptoms. It may also cause stomach problems or pneumonia in the mother during labour. You should discuss the potential risks and benefits for you and your baby with your doctor before you take this medicine.</p>		
<b>Breast-feeding:</b>		
<p>Although dihydrocodeine has not been found in breast milk, it is recommended that you do not take this medicine if you are breast-feeding unless your doctor specifically advises you to do so. Ask your doctor or pharmacist for advice before taking any medicine when you are pregnant or breast-feeding.</p>		
<b>Driving and using machines:</b>		
<p>Do not drive or use any tools or machinery if this medicine makes you drowsy or affects you in any way that would impair your performance of these activities.</p>		

**Taking other medicines:**

Although certain medicines that could interact with the dihydrocodeine in your tablets are listed below, this is not a comprehensive list. Please tell your doctor or pharmacist if you are taking or have recently taken any other medicine, including herbal remedies or others that you have bought yourself, so they can advise you. Your doctor may need to change your dose or your medication.

Medicines that must **not** be taken with Mypaid Tablets:

- **If you are taking or have taken a monoamine oxidase inhibitor (MAOI) within the last 2 weeks (eg phenelzine, isocarboxazid) you should NOT take Mypaid Tablets.**

Medicines that could result in an increased risk of side effects if taken with Mypaid Tablets:

- Medicines containing alcohol.
- Treatments for depression (antidepressants) including amitriptyline, clomipramine, dosulepin, doxepin, imipramine, lofepramine, trimipramine and moclobemide.
- Medicines for schizophrenia, mania or a related disorder such as chlorpromazine, haloperidol, thioridazine, trifluoperazine.
- Medicines that make you feel less anxious including diazepam, lorazepam, buspirone.
- Medicines to help you sleep, for example, temazepam, nitrazepam, zopiclone, zolpidem, chlormethiazole.
- Cimetidine, a treatment for ulcers or heartburn.
- Medicines that inhibit bone marrow production, such as azathioprine.

Medicines that could be less effective if taken with Mypaid Tablets:

- Ciprofloxacin, an antibiotic.
- Domperidone or metoclopramide - treatments for nausea and vomiting.
- Mexiletine, a treatment for heart rhythm abnormalities.
- Ritonavir, for HIV infection.

**3. HOW TO TAKE MYPaid TABLETS.**

Always take Mypaid Tablets exactly as your doctor has instructed you. You should check with your doctor or pharmacist if you are unsure.

The usual dose for adults and children over the age of 12 is to take between 60mg and 120mg every 12 hours.

Elderly patients may need a lower dose than other adults.

Children under 12 should not take this medicine.

Do not chew these tablets.

**If you take more Mypaid Tablets than you should:**

Talk to your doctor or pharmacist if you have accidentally taken any extra tablets. If anyone has taken an overdose of Mypaid Tablets, talk to your doctor immediately, call an ambulance or take them directly to your nearest hospital Accident & Emergency department. Take the tablet container with you even if it is empty.

**If you forget to take Mypaid Tablets:**

Do not take a double dose to make up for a forgotten dose. Take a dose as soon as you remember, unless it is almost time for your next dose. Continue to take the tablets at 12 hour intervals.

**Effects when treatment with Mypaid Tablets is stopped:**

Most patients will not notice any effects when treatment is stopped. In rare instances after longer term treatment, if a patient has become dependent on this medicine, severe withdrawal symptoms may occur if treatment is withdrawn abruptly.

**4. POSSIBLE SIDE EFFECTS.**

Like all medicines, Mypaid Tablets can have side effects.

The most common side effects experienced by people taking these tablets are nausea and vomiting (particularly when first taking the medicine), constipation and drowsiness. Talk to your doctor or pharmacist if you experience any of these effects, particularly if they are troublesome.

Some patients have also experienced vertigo (the room appears to be spinning around you); dizziness; fainting; headache; a contraction of the pupil (the dark bit in the middle of the eye becomes very small); a difficulty in passing water; sudden spasms causing pain in the lower abdomen; more generalised abdominal pain; a feeling of light headedness caused by low blood pressure sometimes causing dizziness on standing; a drop in body temperature possibly associated with fatigue and confusion; a slowing or speeding up of the pulse rate; a feeling that the heart is racing or beating irregularly; a tingling sensation affecting the fingers and toes; confusion; hallucinations; a general feeling of not being well; changes in mood; decreased need for sex and ability to 'perform'; a dry mouth; sweating; a flushed/red face; rashes, possibly like nettle rash, sometimes itchy.

Some patients have noticed that after taking dihydrocodeine for some time the same dose becomes less effective, this may be associated with a need to continue to take the medicine even if it is no longer needed for pain relief.

If you experience any of these side effects talk to your doctor or pharmacist as soon as you notice them.

Larger doses of dihydrocodeine have caused respiratory depression, causing problems with breathing and a fall in blood pressure causing dizziness, a feeling of fatigue and pale skin. **If you suffer from these symptoms call your doctor immediately or phone for an ambulance.**

Although very rare, some people may be allergic to dihydrocodeine. If you notice any symptoms suggesting this, such as swelling of the lips, eyes or tongue sometimes with a rash, or any difficulty in swallowing or breathing **phone for an ambulance immediately.**

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

**5. STORING MYPaid TABLETS**

Keep out of the reach and sight of children.

Store below 25°C.

Do not use after the expiry date stated on the carton or blister.

This leaflet was last amended in March 2006.

This leaflet applies to Mypaid 60mg, 90mg & 120mg SR Tablets only.

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