# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Feminax Tablets

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:

| | |
|---|---|
| Paracetamol | 500.0 mg |
| Codeine Phosphate | 8.0 mg |
| Hyoscine Hydrobromide | 100.0 micrograms |
| Caffeine Monohydrate equivalent to anhydrous caffeine | 50.0 mg |

For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Tablet

A white oval, biconvex tablet with bevelled edges, with a score line on one side. The other side is embossed with ‘Feminax’. The scoreline is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

For the relief of pain and discomfort associated with menstrual periods.

### 4.2 Posology and method of administration

Posology

*Adults:* Adults and girls over 12 years:
Up to 2 tablets every 4 hours.
Not more than 6 tablets in 24 hours.

The duration of treatment should be limited to 3 days and if no effective pain relief is achieved the patients/carers should be advised to seek the views of a physician.

*Elderly persons:* Not applicable.

*Children aged less than 12 years:* Not applicable.

Codeine should not be used in children below the age of 12 years because of the risk of opioid toxicity due to the variable and unpredictable metabolism of codeine to morphine (see sections 4.3 and 4.4).

Method of administration

Oral.

## 4.3 Contraindications

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

Not to be taken by persons suffering from glaucoma.
This product is not intended for the administration to children < 12 years of age.

In all paediatric patients (0-18 years of age) who undergo tonsillectomy and/or adenoidectomy for obstructive sleep apnoea syndrome due to an increased risk of developing serious and life-threatening adverse reactions (see section 4.4).

Codeine is contraindicated in patients with acute asthma, respiratory depression, acute alcoholism, head injuries and raised intra-cranial pressure.

Severe hepatic insufficiency (Child-Pugh >9).

In women during breastfeeding (see section 4.6)

In patients for whom it is known they are CYP2D6 ultra-rapid metabolisers.

## 4.4 Special warnings and precautions for use

If symptoms persist for more than three days consult your doctor as prolonged use without medical supervision could be harmful.

Use with caution in the presence of renal or hepatic dysfunction.

Prolonged regular use, except under medical supervision, may lead to physical and psychological dependence (addiction) and result in withdrawal symptoms, such as restlessness and irritability once the drug is stopped.

Due to hepatotoxicity paracetamol must not be taken at higher doses or longer than recommended. Using longer than recommended may lead to severe hepatic sequela, such as hepatic cirrhosis. An acute or chronic overdose may lead to severe hepatotoxicity, occasionally with lethal outcome (see section 4.9).

Patients suffering from hepatic diseases or infections affecting the liver such as viral hepatitis must consult their physician before taking paracetamol. For those patients hepatic function determinations may be required at periodic intervals during high-dose or long-term therapy, especially in patients with pre-existing hepatic disease.

Patients with hepatic insufficiency (Child-Pugh <9) should use paracetamol with caution.

An elevation of serum alanine aminotransferase (ALT) may occur during the administration of therapeutic doses of paracetamol.

Moderate alcohol intake and concomitant intake of paracetamol leads potentially to an increased risk of liver toxicity.

Patients suffering from renal diseases must consult their physician before taking paracetamol since dosing adjustment may be required. In case of severe renal insufficiency (creatinine clearance <10 ml/min) the physician has to assess critically the benefit/risk ratio of paracetamol use. Dosing adjustment and continuous monitoring must be ensured.

In general, a continuous use of paracetamol especially of paracetamol in combination with other analgesics may lead to permanent renal damage and the risk of renal failure (analgesic nephropathy).

The prolonged use of high doses may lead to liver and kidney damage. Conditions that increase the hepatic oxidative stress and decrease the hepatic glutathione reserve such as a variety of concomitant drugs, alcoholism, sepsis, or diabetes mellitus may place the patient at increased risk of hepatic toxicity to paracetamol at therapeutic doses.

Very rare cases of serious skin reactions have been reported. In the event of skin reddening, rash, blisters or peeling, discontinue paracetamol use and seek medical attention immediately (see section 4.8).

Use of paracetamol by patients suffering from Gilbert syndrome may lead to more pronounced hyperbilirubinemia and clinical symptoms thereof such as jaundice. Thus, these patients should use paracetamol with caution.

Concomitant intake of other drugs containing paracetamol should be avoided.

Patients with hereditary glucose-6-phosphate-dehydrogenase deficiency should consult their physician before taking paracetamol (risk of hemolytic anemia).

The hazards of paracetamol overdose are greater in those with non-cirrhotic alcoholic liver disease.

Immediate medical advice should be sought in the event of an overdose, even if the patient feels well, because of the risk of delayed, serious liver damage.

Care should be observed in administering the products to any patients whose condition may be exacerbated by opioids, those on concurrent CNS depressant drugs and those with inflammatory or obstructive bowel disorders.

In cases of renal insufficiency the rate of excretion of codeine and paracetamol metabolites may be reduced, and dosage schedules may need to be revised accordingly.

Prolonged use of any type of painkiller for headaches can make them worse. If this situation is experienced or suspected, medical advice should be obtained and treatment should be discontinued. The diagnosis of ‘Medication Overuse Headache’ should be suspected in patients who have frequent or daily headaches despite (or because of) the regular use of headache medications.

Codeine is metabolised by the liver enzyme CYP2D6 into morphine, its active metabolite. If a patient has a deficiency or is completely lacking this enzyme an adequate analgesic effect will not be obtained. Estimates indicate that up to 7% of the Caucasian population may have this deficiency. However, if a patient is an extensive or ultra-rapid metaboliser there is an increased risk of developing side effects of opioid toxicity even at commonly prescribed doses. These patients convert codeine into morphine rapidly resulting in higher than expected serum morphine levels.

General symptoms of opioid toxicity include confusion, somnolence, shallow breathing, small pupils, nausea, vomiting, constipation and lack of appetite. In severe cases this may include symptoms of circulatory and respiratory depression, which may be life-threatening and very rarely fatal.

Estimates of prevalence of ultra-rapid metabolisers in different populations are summarized below:

| Population | Prevalence % |
|---|---|
| African/Ethiopian | 29% |
| African American | 3.4% to 6.5% |
| Asian | 1.2% to 2% |
| Caucasian | 3.6% to 6.5% |
| Greek | 6.0% |
| Hungarian | 1.9% |
| Northern European | 1% to 2% |

Limited evidence suggests that individuals who are ultra-rapid metabolizers may convert codeine to its active metabolite, morphine, more rapidly and completely than other people. Patients may experience overdose symptoms such as extreme sleepiness, confusion, shallow breathing or severe constipation. This can also result in higher than expected serum and breast milk morphine levels (see “Fertility, pregnancy and lactation”).
There have been reports in the published literature that codeine given post-operatively in children after tonsillectomy and/or adenoidectomy for obstructive sleep apnoea, led to rare, but life-threatening adverse events including death (see also section 4.3).

All children received doses of codeine that were within the appropriate dose range; however there was evidence that these children were either ultra-rapid or extensive metabolisers in their ability to metabolise codeine to morphine.

Codeine is not recommended for use in children in whom respiratory function might be compromised including neuromuscular disorders, severe cardiac or respiratory conditions, upper respiratory or lung infections, multiple trauma or extensive surgical procedures. These factors may worsen symptoms of morphine toxicity.

The elderly and patients under medical care (in particular those with urinary retention, or with cardiovascular, metabolic, gastrointestinal, liver or renal disease, or suffering from CNS disorders such as seizures) should consult a doctor before taking hyoscine hydrobromide.

Hyoscine hydrobromide may cause drowsiness. Children taking this medicine should not be left unattended.

Hearing loss has been reported for paracetamol and codeine combination products in the context of prolonged use and at higher than recommended doses.

Avoid alcoholic drink.

Do not exceed the stated dose.

This product should be kept out of the sight and reach of children.

## 4.5 Interaction with other medicinal products and other forms of interaction

**Paracetamol:**
Drugs leading to delayed gastric emptying, e.g. after use of propantheline or colestyramine, may lead to slower absorption of paracetamol and thus to a delay in the onset of action.

Drugs leading to accelerated gastric emptying, e.g. after use of metoclopramide or domperidone, may lead to faster absorption of paracetamol and thus to an acceleration in the onset of action.

Concomitant use of drugs which cause enzyme induction in the liver, e.g. certain hypnotics and antiepileptics (glutethimide, phenobarbital, phenytoin, carbamazepine etc.) or rifampicin may lead to liver damage even after paracetamol doses which would otherwise be harmless. In case of alcohol abuse, taking paracetamol, even in therapeutic dosages, may result in liver damage.

The effects of the following are intensified: combination with chloramphenicol may prolong the half-life of chloramphenicol and thus potentially increase its toxicity.

Paracetamol (or its metabolites) interferes with enzymes involved in vitamin K-dependent coagulation factor synthesis. Interactions between paracetamol and warfarin or coumarin derivatives may lead to an elevated international normalized ratio and an increased risk of bleeding. Patients on oral anticoagulants should therefore not take paracetamol for long periods without medical supervision.

Tropisetron and granisetron, 5-hydroxytryptamine type 3 antagonists, may totally inhibit the analgesic effect of paracetamol through a pharmacodynamic interaction.

Simultaneous use of paracetamol and AZT (zidovudine) increases the tendency towards a reduction in the white blood cell count (neutropenia). Paracetamol should therefore not be taken together with AZT, except on medical advice.

**Codeine phosphate:**
The effects of central nervous system depressants (including alcohol) may be potentiated by codeine.

**Hyoscine hydrobromide:**
The effects of hyoscine hydrobromide may be enhanced by other drugs with anticholinergic properties (including amantadine, classical antihistamines, phenothiazine antipsychotics and tricyclic antidepressants), therefore, combining these drugs with hyoscine should be avoided.

The sedative effect of hyoscine hydrobromide may be enhanced with alcohol or CNS depressants.

The reduction in gastric motility caused by hyoscine hydrobromide may affect the absorption of other drugs.

## 4.6 Fertility, pregnancy and lactation

### 4.6.1. Pregnancy

Feminax tablets should only be used during pregnancy on advice of a doctor when the potential benefits outweigh the risks.

Paracetamol:
A large amount of data on pregnant women indicate neither malformative, nor feto/neonatal toxicity. Paracetamol can be used during pregnancy if clinically needed however it should be used at the lowest effective dose for the shortest possible time and at the lowest possible frequency.

Codeine:
While selective use of this medication may be considered during pregnancy, there is a risk of respiratory depression in the newborn if large doses are taken before delivery, and there is risk of withdrawal symptoms in the newborn in the event of chronic maternal intake at the end of pregnancy. Codeine should only be used in pregnancy under the recommendation of a doctor, and is reserved for cases where the potential benefits outweigh the risks.

Hyoscine hydrobromide:
The safety of hyoscine hydrobromide in pregnancy has not been established. It should only be used during pregnancy, particularly in the first trimester, if the expected benefit to the mother outweighs the potential risk to the developing foetus and on advice of a doctor.

### 4.6.2. Lactation

Feminax tablets should not be used in breastfeeding.

Paracetamol:
Paracetamol passes into breast milk in small quantities. Although no undesirable effects have been observed until now, paracetamol should be used during breastfeeding only upon doctor’s advice.

Codeine phosphate: Codeine-containing products should not be taken by nursing mothers due to risk of respiratory depression in infants.
At normal therapeutic doses codeine and its active metabolites may be present in breast milk at very low doses and are unlikely to adversely affect the breast fed infant.

However, if the patient is an ultra-rapid metaboliser of CYP2D6, higher levels of the active metabolite, morphine, may be present in breast milk and on very rare occasions may result in symptoms of opioid toxicity in the infant, which may be fatal.

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

Hyoscine hydrobromide:
Caution is required during lactation as small amounts of hyoscine hydrobromide may pass into breastmilk.

## 4.7 Effects on ability to drive and use machines

May cause drowsiness. If affected do not drive or operate machinery.

## 4.8 Undesirable effects

**Paracetamol:**
The listed adverse drug reactions are based on spontaneous reports, thus an organization according to CIOMS III categories of frequency is not possible.

**Blood and lymphatic system disorders**
Changes in blood count including thrombocytopenia, thrombocytopenic purpura, leukopenia, and pancytopenia.

**Gastrointestinal disorders**
Nausea, vomiting, stomach discomfort, diarrhoea, and abdominal pain.

**Hepatobiliary disorders**
Hepatic impairment, hepatitis, as well as dose-dependent hepatic failure, hepatic necrosis (including with fatal outcome). Chronic unapproved use may lead to hepatic fibrosis, hepatic cirrhosis including with fatal outcome (see sections 4.4. and 4.9.)

**Immune system disorders**
Allergic reactions, anaphylactic reaction, and anaphylactic shock.

**Nervous system disorders**
Dizziness, somnolence.

**Renal and urinary disorders**
Renal damage especially in case of overdose.

**Respiratory, thoracic and mediastinal disorders**
Bronchospasm and asthma including analgesic asthma syndrome.

**Skin and subcutaneous tissue disorders**
Very rare cases of serious skin reactions have been reported.
Rash, pruritus, urticaria, allergic edema and angioedema, acute generalized exanthematous pustulosis, fixed drug eruption, erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis (including with fatal outcome).

**Codeine phosphate:**
Codeine may sometimes cause constipation.

**Hyoscine hydrobromide:**
The listed adverse drug reactions are based on spontaneous reports, thus an organization according to CIOMS III categories of frequency is not pertinent.

**Eye disorders**
Blurred vision, mydriasis.

**Gastrointestinal disorders**
Dry mouth.

**Immune System Disorders**
Allergic reaction and anaphylactic reaction. Hypersensitivity reactions with respective laboratory and clinical manifestations, including asthma syndrome, mild to moderate reactions affecting skin, respiratory tract, and cardiovascular system, and symptoms such as rash, urticaria, oedema, pruritus, cardio-respiratory distress, have been reported.

**Nervous system disorders**
Drowsiness, dizziness, sedation and somnolence are commonly reported. Central nervous system stimulation including restlessness, hallucinations and confusion, has been less frequently reported following administration of hyoscine hydrobromide.

**Caffeine:**
High doses of caffeine may cause tremors and palpitations.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

## 4.9 Overdose

**Paracetamol:**
In case of overdose, contact a physician or poison control center immediately. Prompt medical attention is critical for adults as well as children even if no signs and/or symptoms are apparent.

Acute toxicity
The most important effect of acute intoxication is hepatotoxicity: hepatocellular damage is caused by the binding of reactive paracetamol metabolites to liver cell proteins. In therapeutic doses these metabolites are bound by glutathione, forming non-toxic conjugates. In the event of massive overdose the liver's supply of SH-donors (which promote glutathione formation) is exhausted, toxic metabolites accumulate and liver cell necrosis occurs, with consequent impairment of liver function progressing to hepatic coma. Renal damage as a result of renal tubular necrosis has also been described independently.

The overdose threshold may be lowered in patients taking certain medicines or alcohol, or are seriously undernourished.

Chronic toxicity
Chronic toxicity includes diverse hepatic impairments (see Symptoms of intoxication). The data regarding the chronic toxicity and particularly the nephrotoxicity of paracetamol are controversial. Attention should be paid to the possible influence on peripheral blood cell count with chronic intake.

Symptoms of intoxication
The onset of acute intoxication is characterized by nausea, vomiting, abdominal pain, sweating and general malaise. The patient's condition may improve for 24 to 48 hours, although the symptoms may not disappear completely.

The size of the liver increases rapidly, transaminases and bilirubin are elevated, prothrombin time becomes pathological, urinary output falls, slight azotemia may develop. Hypokalemia and metabolic acidosis (including lactic acidosis) may develop in the setting of acute and/or chronic overdose. Frequent clinical manifestations after 3 to 5 days are jaundice, fever, fetor hepaticus, haemorrhagic diathesis, hypoglycaemia, and liver failure. Hepatic failure may progress to all stages of hepatic encephalopathy, 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.

Treatment of intoxication
Medical intensive care with close monitoring of vital signs, laboratory findings and circulatory status should generally be initiated. If intoxication with paracetamol is suspected an intravenous administration of SH-group donors (e.g. methionine, cysteamine or N-acetylcysteine) is useful within 10 hours of ingestion as they conjugate the reactive metabolites and thus aid their normal detoxification. N-acetylcysteine can be protective to a certain degree up to 48 hours after ingestion. Gastric lavage is useful within the first six hours. Haemodialysis and haemoperfusion support elimination of the substance. It is recommended to control the plasma concentration of paracetamol.

**Codeine phosphate:**
The toxic effects of codeine may be reversed by the administration of naloxone injection.

**Hyoscine hydrobromide:**
The symptoms of overdosage are tachycardia, arrhythmia, blurring of vision, photophobia, and urinary retention.

Drowsiness is usual but paradoxical stimulation with hallucinations may occur.
Treatment: gastric lavage or induced emesis and symptomatic treatment.

# 5 PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

Pharmacotherapeutic group:
Paracetamol: Other analgesics and antipyretics
Codeine: Opioids
Hyoscine hydrobromide: Antiemetics and antinauseants
Caffeine: Psychostimulants, agents used for ADHD and nootropics.

ATC-Codes: N02AA59

**Paracetamol:**
Paracetamol, a para-aminophenol derivative, has analgesic and antipyretic properties and weak antiinflammatory activity.

The mechanism of analgesic action has not been fully determined. Paracetamol may act predominantly by inhibiting prostaglandin synthesis in the central nervous system (CNS) and, to a lesser extent, through a peripheral action by blocking pain-impulse generation. The peripheral action may also be due to inhibition of prostaglandin synthesis or to inhibition of the synthesis or actions of other substances that sensitize pain receptors to mechanical or chemical stimulation.

Paracetamol probably produces antipyresis by acting centrally on the hypothalamic heat-regulating center to produce peripheral vasodilation resulting in increased blood flow through the skin, sweating, and heat loss. The central action may involve inhibition of prostaglandin synthesis in the hypothalamus.

**Codeine phosphate:**
Codeine is a centrally acting weak analgesic. Codeine exerts its effect through μ opioid receptors, although codeine has low affinity for these receptors, and its analgesic effect is due to its conversion to morphine. Codeine, particularly in combination with other analgesics such as paracetamol, has been shown to be effective in acute nociceptive pain.

**Hyoscine hydrobromide:**
Competitively inhibits muscarinic receptors for acetylcholine and acts as a nonselective muscarinic antagonist, producing both peripheral antimuscarinic properties and central sedative, antiemetic, and amnestic effects. This

alkaloid is the most effective single agent to prevent motion sickness.

**Caffeine:** CNS stimulant.

## 5.2 Pharmacokinetic properties

**Paracetamol:**
Absorbed rapidly and completely after oral administration. Maximum serum concentrations are reached after 0.5-1.5 hours.

The plasma half-life after oral administration is 1.5-2.5 hours. The plasma protein binding of paracetamol is low. Over 80% of the paracetamol is eliminated within 24 hours. Elimination is delayed in patients with impaired liver or kidney function.

After enzymatic transformation in the liver paracetamol is eliminated exclusively by the kidneys, mainly in the form of glucuronic acid and sulphuric acid conjugates. Only about 1-3% is eliminated in the form of the free parent substance.

**Codeine Phosphate:**
Absorbed from GI tract. Peak plasma concentration about 1 hour after ingestion. Metabolised by o- and n-demethylation in liver. Excreted almost entirely by kidney mainly as conjugates with glucuronic acid. Plasma half life 3-4 hours.

**Hyoscine Hydrobromide:**
Hyoscine hydrobromide is absorbed rapidly, but variably and incompletely from the gastrointestinal tract. The mean time to peak drug concentration is approximately 24 minutes following administration. The oral bioavailability has been reported to be only 13%. Pharmacological effects on the GI tract (decreased motility and decreased gastric secretion), and intestinal metabolism (see below) may also contribute to the limited oral bioavailability. Approximately 30% of hyoscine in the plasma is bound to protein. The elimination half life is estimated at approximately 1 hour.

Limited human data regarding the metabolism of hyoscine are available, however, since only a small proportion (2.6%) of pharmacologically active drug is excreted in the urine, a first pass metabolism is theorized. While the metabolic profile has not been fully elucidated, it is suggested that glucuronide and/or sulfate conjugation are significant metabolic pathways. In addition, it appears that oxidative demethylation of the drug via CYP3A, probably occuring in the intestinal mucosa, is also involved. In a study in healthy volunteers, the administration of hyoscine with grapefruit juice, an inhibitor of CYP3A, increased the $AUC_{0\text{-}24h}$ and prolonged the time to peak concentration, resulting in a higher drug bioavailability.

**Caffeine:**
Readily absorbed after oral administration and is widely distributed throughout the body. Caffeine passes readily into the CNS and into the saliva.

It is metabolised almost completely in the liver via oxidation, demethylation, and acetylation. It is excreted in the urine as 1-methyluric acid, 1-methylxanthine, 7-methylxanthine and other metabolites. Elimination half-lives are approximately 3 to 7 hours in adults.

## 5.3 Preclinical safety data

None.

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

Sodium Starch Glycolate type A
Purified Talc
Gelatin Powder
Stearic Acid
Sodium Lauryl sulfate

## 6.2 Incompatibilities

Not applicable.

## 6.3 Shelf life

30 months

## 6.4 Special precautions for storage

Do not store above 25$^{o}$C.

## 6.5 Nature and contents of container

Hard temper aluminium foil/non toxic food quality PVC blisters. Two blister strips of 10 tablets are packed in a carton.

Pack size: 20 tablets.

## 6.6 Special precautions for disposal and other handling

No special requirements.

## 7 MARKETING AUTHORISATION HOLDER

Bayer Ltd
The Atrium
Blackthorn Road
Dublin 18
Ireland

## 8 MARKETING AUTHORISATION NUMBER

PA1410/045/001

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

Date of first authorisation: 09 February 1983

Date of last renewal: 09 February 2008

## 10 DATE OF REVISION OF THE TEXT

August 2016