Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Veganin Plus Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains
Paracetamol 500mg
Caffeine 30mg
Codeine Phosphate 8mg

For excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.
White, capsule-shaped tablet with dimensions of 17.55 mm x 7.5 mm and debossed on one face to read PCC.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Codeine is indicated in patients older than 12 years of age for the treatment of acute moderate pain which is not considered to be relieved by other analgesics such as paracetamol or ibuprofen oalone.
Suitable for migraine, headache, rheumatic pain, period pain, toothache and neuralgia.

4.2 Posology and method of administration

For oral administration only.

Adults (including the Elderly):

2 tablets taken with water every 4-6 hours.
No more than 8 tablets in 24 hours.

Paediatric population:
Children aged 16 - 18 years:
1-2 tablets taken with water every 6 hours when necessary. Not more than 8 tablets in 24 hours.

Children aged 12 - 15 years:
1 tablet taken with water every 6 hours when necessary. Not more than 4 tablets in 24 hours.

Children aged less than 12 years:
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).
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.

4.3 Contraindications

Hypersensitivity to paracetomol, caffeine, codeine or any of the other constituents. Conditions where morphine and opioids are contraindicated, e.g. acute asthma, respiratory depression, risk of paralytic ileus acute alcoholism, head injuries, raised intra-cranial pressure and following biliary tract surgery.

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)

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

Care is advised in the administration of paracetamol to patients with severe renal or severe hepatic impairment. The hazard of overdose is greater in those with non-cirrhotic alcoholic liver disease.

Care should be taken in administering the product to any patient whose condition may be exacerbated by opioids, particularly the elderly, in whom there is increased sensitivity to the central and gastro-intestinal effects, those on concurrent treatment with other CNS depressant drugs, those with prostatic hypertrophy and those with inflammatory or obstructive bowel disorders. Patients with obstructive bowel disorders or acute abdominal conditions should consult a doctor before using this product.

Patients with a history of cholecystectomy should consult a doctor before using this product as it may cause acute pancreatitis in some patients.

Caution is advised if paracetamol is administered concomitantly with flucloxacillin due to increased risk of high anion gap metabolic acidosis (HAGMA), particularly in patients with severe renal impairment, sepsis, malnutrition and other sources of glutathione deficiency (e.g. chronic alcoholism), as well as those using maximum daily doses of paracetamol. Close monitoring, including measurement of urinary 5-oxoproline, is recommended.

Patients should be advised not to exceed the recommended dose as taking a painkiller for headaches too often or for too long can make them worse.

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. Patients should be advised that they should not take this product for more than 3 days continuously without consulting a doctor.

Excessive intake of caffeine (e.g. coffee, tea and some canned drinks) should be avoided while taking this product (see section 4.9: Overdose caffeine).

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

If symptoms persist, patients should consult a doctor.

Keep of the reach and sight of children.

The label will state:

Front of pack
- Can cause addiction
- For three days use only

Back of pack
- List of indications as agreed in 4.1 of the SmPC
- If you need to take this medicine continuously for more than three days you should see your doctor or pharmacist.
- This medicine contains codeine which can cause addiction if you take it continuously for more than three days. If you take this medicine for headaches for more than three days it can make them worse.

The leaflet will state:

Headlines section (to be prominently displayed)
- This medicine can only be used for …….. (indications)
- You should only take this product for a maximum of three days at a time. If you need to take it for longer than three days you should see your doctor or pharmacist for advice.
- This medicine contains codeine which can cause addiction if you take it continuously for more than three days. This can give you withdrawal symptoms from the medicine when you stop taking it.
- If you take this medicine for headaches for more than three days it can make them worse.

Section 1: What the medicine is for
- Succinct description of the indications from 4.1 of the SmPC

Section 2: Before taking
- This medicine contains codeine which can cause addiction if you take it continuously for more than three days. This can give you withdrawal symptoms from the medicine when you stop taking it.
- If you take a painkiller for headaches for more than three days it can make them worse.

Section 3: Dosage
- Do not take for more than 3 days. If you need to use this medicine for more than three days you must speak to your doctor or pharmacist.
- This medicine contains codeine and can cause addiction if you take it continuously for more than three days. When you stop taking it you may get withdrawal symptoms. You should talk to your doctor or pharmacist if you think you are suffering from withdrawal symptoms.

Section 4: Side effects

Some people may have side-effects when taking this medicine. If you have any unwanted side-effects you should seek advice from your doctor, pharmacist or other healthcare professional. The health Products Regulator Authority encourages patients to report any unwanted side effects 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

Insert a new paragraph as follows:

How do I know if I am addicted?

If you take the medicine according to the instructions on the pack it is unlikely that you will become addicted to the medicine. However, of the following apply to you it is important that you talk to your doctor:

- You need to take the medicine for longer periods of time.
- You need to take more than the recommended dose.
- When you stop taking the medicine you feel very unwell but you feel better if you start taking the medicine again.

CYP2D6 metabolism
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 the 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%-2%

Post-operative use in children
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.

Children with compromised respiratory function
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.

4.5 Interaction with other medicinal products and other forms of interactions

Paracetamol:

The speed of absorption of paracetamol may be increased by metoclopramide or domperidone and absorption reduced by cholestyramine. Cholestyramine should not only be administered not less than one hour after taking paracetamol.

The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular use of paracutamol with increased risk of bleeding. Occasional doses have no significant effect.

The use of drugs which induce hepatic microsomal enzymes, such as anticonvulsants and oral contraceptive steroids, may increase the extent of metabolism of paracetamol, resulting in reduced plasma concentration of the drug and a faster elimination rate.

Caution should be taken when paracetamol is used concomitantly with flucloxacillin as concurrent intake has been associated with high anion gap metabolic acidosis, especially in patients with risks factors (see section 4.4)

Drugs which induce hepatic microsomal enzymes, such as alcohol and barbiturates, may increase the hepatotoxicity of paracetamol, particularly after overdosage.
There is limited evidence suggesting that paracetamol may affect chloramphenicol pharmacokinetics but its validity has been criticised and evidence of a clinically relevant interaction appears to be lacking. Although no routine monitoring is needed, it is important to bear in mind this potential interaction when these two medications are concomitantly administered, especially in malnourished patients.

Codeine:

CNS depression or excitation may occur if codeine is given to patients receiving monoamine oxidase inhibitors, or within two weeks of stopping treatment with them. The effects of CNS depressants (including alcohol) may be potentiated by codeine.

Concurrent use of codeine with antidiarrhoeal and antiperistaltic agents may increase the risk of severe constipation. Concomitant use of antimuscarinics or medications with antimuscarinic action may result in an increased risk of severe constipation, which may led to paralytic ileus and or/urinary retention.

Quinidine can inhibit the analgesic effect of codeine.

Codeine may delay the absorption of mexiletine and thus reduce the antiarrhythmic effect of the latter. Codeine may antagonise the gastrointestinal effects of metoclopramide and domperidone. Cimetidine inhibits the metabolism of opioid analgesics resulting in increased plasma concentrations.

Naltrexone blocks the therapeutic effect of opioids.

Caffeine:

Caffeine, a CNS stimulant, has an antagonistic effect towards the action of sedatives and tranquilisers (e.g. benzodiazepine and non-benzodiazepine hypnotics).

Caffeine may enhance the tachycardiac effect of some decongestant (e.g. ephedrine and pseudoephedrine).

4.6 Fertility, pregnancy and lactation

Regular use of codeine during pregnancy may cause physical dependence in the foetus leading to withdrawal symptoms in the neonate. Administration of codeine during labour may depress respiration in the neonate. Opioid analgesics may cause gastric stasis during labour, increasing the risk of inhalation pneumonia in the mother.
Codeine should not be used during breastfeeding (see section 4.3).
At normal therapeutic doses codeine and its active metabolite 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 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.

Epidemiological studies in human pregnancy have shown no ill effects due to caffeine use in the recommended dosage, but patients should follow medical advice regarding its use.

Epidemiological studies on neurodevelopment in children exposed to paracetamol in utero show inconclusive results.

Paracetamol is excreted in breast milk, but not in a clinically significant amount.

4.7 Effects on ability to drive and use machines

Patients should not drive or operate machinery if affected by drowsiness.

4.8 Undesirable effects

Paracetamol:

Adverse effects of paracetamol are rare, but hypersensitivity including skin rash may occur. There have been a few reports of blood dyscrasias including thrombocytopenia and agranulocytosis, but these were not necessarily causally related to paracetamol.

Respiratory, thoracic and mediastinal disorders such as bronchospasm in patients sensitive to aspirin and others NSAIDs are very rare. Hepatobiliary disorders such as hepatic dysfunction is very rare.

Skin and subcutaneous tissue disorders such as cutaneous hypersensitivity reactions including pruritus, sweating, purpura, urticarial and angioedema are very rare. Very rare cases of serious skin reactions have also been reported.

Renal and urinary disorders such as sterile pyuria (cloudy urine) is very rare.

Caffeine:

High doses of caffeine may produce headache, tremor, nervousness, dizziness and irritability. The frequency of these is unknown.

Codeine:

Codeine can produce constipation and drowsiness. Occasional effects are nausea, vomiting, dyspepsia, acute pancreatitis in patients with a history of cholecystectomy, sweating, facial flushing, dry mouth, blurred or double vision, dizziness, postural

hypotension, headache, vertigo, palpitations, allergic reactions (itch, skin rash, facial oedema), and difficulties in micturition (dysuria, increased frequency, decrease in amount).

Side-effects which occur rarely include hallucinations, nightmares, restlessness and stomach cramps. The frequency and severity are determined by dosage, duration of treatment and individual sensitivity and are unlikely at this dosage. Tolerance and dependency can occur, especially with prolonged high doses of codeine. See also Section 4.9 'Overdose'.

High doses of caffeine may produce headache, tremor, nervousness and irritability.

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
Liver damage is possible in adults who have taken 10g or more of paracetamol
It is considered that excess quantities of a toxic metabolite (usually adequately detoxified by glutathione when normal doses of paracetamol are ingested) become irreversibly bound to liver tissue. 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

- Is on long term treatment with carbamazepine, phenobarbitone, phenytoin, primidone, rifampicin, St John's Wort or other drugs that induce live enzymes.

Or

- Regularly consumes ethanol in excess of recommended amounts.

Or

- Is likely to be glutathione deplete e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia.

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, coma and death. Acute renal failure with acute tubular necrosis may develop even in the absence of severe liver damage. Cardiac arrhythmias and pancreatitis have been reported.

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.

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) but results should not delay initiation of treatment beyond 8 hours after ingestion, as the effectiveness of the antidote declines sharply after this time. Activated charcoal should not be used if it is anticipated that oral methionine will be given to the patient. 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.

Codeine

The effects in codeine overdosage will be potentiated by simultaneous ingestion of alcohol and psychotropic drugs.

Codeine overdose associated with central nervous system depression, including respiratory depression, may develop but is unlikely to be severe unless other sedative agents have been co-ingested, including alcohol, or the overdose is very large. The pupils may be pin-point in size; nausea and vomiting are common. Hypotension and tachycardia are possible but unlikely. Symptoms of codeine overdose also include cold clammy skin, confusion, convulsions, dizziness, drowsiness, nervousness or restlessness, miosis, bradycardia, dyspnoea, unconsciousness and weakness.

Management of codeine overdose should include general symptomatic and supportive measures including a clear airway and monitoring of vital signs
until stable. Consider activated charcoal if an adult presents within one hour of ingestion more than 350 mg or a child more than 5 mg/kg. Give naloxone if coma or respiratory depression is present. Naloxone is a competitive antagonist and has a short half-life so large and repeated doses may be required in a seriously poisoned patient. A dose of 0.4-2mg is given intravenously or intramuscularly to adults, this is repeated at intervals of 2-3 minutes if necessary up to 10mg naloxone may be given. Observe for at least four hours after ingestion, or eight hours if a sustained release preparation has been taken. Codeine is not dialyzable.

Caffeine

Caffeine overdose may cause diuresis, tachycardia, irritability, nervousness, restlessness, gastrointestinal disturbance and CNS stimulation such as agitation, excitement, insomnia and tremors. Lethal doses of caffeine tend to be between 5 - 10g. The management of caffeine toxicity is generally symptomatic and supportive (e.g. hydration). For acute ingestion, emesis or gastric lavage is advised.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharacetamol has analgesic, antipyretic and mild anti-inflammatory properties. It inhibits prostaglandin synthesis, especially in the Central Nervous System.Paracetamol does not inhibit chronic inflammatory reactions.

Caffeine acts on the Central Nervous System, on muscle, including the cardiac muscle and on the kidneys.Its action on the CNS is mainly on the higher centres and produces a condition of wakefulness and increased mental activity.

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.

5.2 Pharmacokinetic properties

Paracetamol is rapidly absorbed from the upper gastrointestinal tract after oral administration with the small intestine being an important site of absorption. Paracetamol is satisfactorily absorbed from the rectum, but with greater variation than following oral administration.

Peak blook levels of 15-20 micrograms per ml after normal 1g doses of paracetamol occur within 30-60 minutes depending on dosage form. It is rapidly distributed throughout the body and is primarily metabolised in the liver with exertion via the kidney. Elimination half –life is about 2 hours after reaching a peak following a 1g oral dose.

Caffeine is absorbed readily after oral administration, but absorption from the gastrointestinal tract may be erratic. There is little evidence of accumulation in any particular tissue.

Caffeine passes readily into the Central Nervous System and into saliva; concentrations have also been detected in breast milk. Caffeine is metabolised almost completely and is excreted via the kidney. Caffeine has a plasma half-life of approximately 3.5 hours and peak plasma concentrations may occur some 50-75 minutes after oral administration.

Codeine Phosphate is absorbed from the gastrointestinal tract. Ingestion of Codeine Phosphate produces peak plasma concentrations in approximately 1 hour. Codeine is metabolised in the liver and the metabolites are excreted almost entirely by the kidney, largely as inactive forms. The half-life Codeine in plasma is 2-4 hours.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.

Conventional studies using the currently accepted standards for the evaluation of toxicity to reproduction and development are not available for paracetamol.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize starch
Methylcellulose
Povidone
Water, Purified
Talc
Calcium stearate

Film Coating
Hypromellose (5)
Hypromellose (15)
Polyethylene glycol 3350

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 25°C.Store in the original package.

6.5 Nature and contents of container

250 micron opaque white UPVC/20 micron aluminium foil blister inside a carton.

OR

30 micron pyramidally embossed hard temper aluminium (with 250 micron PVC blisters) inside a carton.

OR

35/9 paper/foil with PVC blister inside a carton.

8 tablets per blister, either 1, 2, 3 or 4 strips per carton.

OR

10 tablets per blister, either 1, 2 or 3 strips per carton.

OR

12 tablets per blister strip, either 1 or 2 strips per carton.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

None

7 MARKETING AUTHORISATION HOLDER

Chefaro Ireland DAC
The Sharp Building
Hogan Place
Dublin 2
Ireland

8 MARKETING AUTHORISATION NUMBER

PA1186/006/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27September 2002
Date of last renewal: 19 July 2006

10 DATE OF REVISION OF THE TEXT

May 2022