Brand Name : VON-P CAPSULES	
Generic Name : Ibuprofen, Paracetamol and Caffeine Capsules	

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ibuprofen, Paracetamol and Caffeine Capsules (VON-P Capsules)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard gelatin capsules contains:

Ibuprofen BP	200mg
Paracetamol BP	325mg
Caffeine (Anhydrous) BP	30mg
Excipients	q.s.

Approved colour used in capsule shells

3. PHARMACEUTICAL FORM

Hard Gelatine Capsules

A light blue / dark blue hard gelatin capsules of size "0" containing white colored powder.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

- Rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, cervical spondylosis, intervertebral disc syndrome and sciatica
- Non-articular rheumatic conditions including fibrositis, myositis, bursitis and low back pain
- Soft tissue injuries such as sprains, strains and sports injuries
- Painful inflammatory conditions in gynaecology
- Post-operative and post-traumatic inflammation
- Pain and inflammation following surgery
- Acute gout
- Severe headache

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4.2. Posology and method of administration

For oral administration and short term-use only.
The lowest effective dose should be used for the shortest time necessary to relieve symptoms. The patient should consult a doctor if the symptoms persist or worsen or if the product is required for more than 3 days.

Adults: One Capsule to be taken up to three times per day with water. Leave at least six hours between doses.
If the one tablet dose does not control symptoms, a maximum of two Capsules may be taken up to three times a day. Leave at least six hours between doses.
Do not take more than six tablets (3000mg Paracetamol, 1200mg Ibuprofen) in any 24 hours period.
To minimise side effects, it is recommended that patients take Nuromol with food.

Elderly: No special dosage modifications are required (see section 4.4).
The elderly are at increased risk of the serious consequences of adverse reactions. If an NSAID is considered necessary, the lowest effective dose should be used for the shortest possible duration. The patient should be monitored regularly for gastrointestinal bleeding during NSAID therapy.
Not for use by children under 18 years.

4.3. Contraindications

It may not be recommended to consume VON-P Capsules if you have the following diseases, medical or physical conditions:

- Active peptic ulcer
- Aspirin
- Breastfeeding
- Gastrointestinal bleeding

4.4. Special warnings and precautions for use

The hazard of paracetamol overdose is greater in patients 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.
Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see Section 4.2, and gastrointestinal and cardiovascular risks below) and by patients taking the dose with food (see Section 4.2).
Elderly:

The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal (see Section 4.2).
Caution is required in patients with certain conditions:

• *Respiratory disorders:*

In patients suffering from, or with a history of, bronchial asthma or allergic disease NSAIDs have been reported to precipitate bronchospasm.
• *Cardiovascular, renal and hepatic impairment:*

The administration of NSAIDs may cause a dose dependent reduction in prostaglandin formation and precipitate renal failure. Patients at greatest risk of this reaction are those with impaired renal function, cardiac impairment, liver dysfunction, those taking diuretics and the elderly. Renal function should be monitored in these patients (see Section 4.3).
• *Cardiovascular and cerebrovascular effects*

Appropriate monitoring and advice are required for patients with a history of hypertension and/or mild to moderate congestive heart failure as fluid retention and oedema have been reported in association with NSAID therapy.
Clinical trial data suggest that use of ibuprofen, particularly at high doses (2400 mg daily) and in long-term treatment may be associated with a small increased risk of arterial thrombotic events (e.g. myocardial infarction or stroke). Overall, epidemiological studies do not suggest that low dose ibuprofen (e.g. ≤1200mg daily) is associated with an increased risk of myocardial infarction.
Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with ibuprofen after careful consideration. Similar consideration should be made before initiating long-term treatment for patients with risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking).

• *Gastrointestinal bleeding, ulceration and perforation:*

Gastrointestinal (GI) bleeding, ulceration and perforation, which can be fatal, has been reported with all NSAIDs at anytime during treatment, with or without warning symptoms or a previous history of serious GI events.
The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (see Section 4.3) and in the elderly. These patients should commence treatment on the lowest dose available. Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low dose acetylsalicylic acid, or other drugs likely to increase gastrointestinal risk (see below and 4.5).
Patients with a history of GI toxicity, particularly the elderly, should report any unusual abdominal symptoms (especially GI bleeding) particularly in the initial stages of treatment.
Caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin selective serotonin-reuptake inhibitors or antiplatelet agents such as acetylsalicylic acid (see Section 4.5).

When GI bleeding or ulceration occurs in patients receiving ibuprofen containing products, the treatment should be withdrawn.

NSAIDs should be given with care to patients with a history of GI disease (ulcerative colitis, Crohn's disease) as these conditions may be exacerbated (see Section 4.8).

• *SLE and mixed connective tissue disease:*

In patient with systemic lupus erythematosus (SLE) and mixed connective tissue disease disorders there may be an increased risk of aseptic meningitis (see Section 4.8).

• *Dermatological:*

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs (see Section 4.8). Patients appear to be at highest risk of these reactions early in the course of therapy, the onset of the reaction occurring in the majority of cases within the first month of treatment. Use of this product should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

• *Impaired female fertility:*

The use of the product may impair female fertility and is not recommended in women attempting to conceive. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of the product should be considered.

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

Medicine and salt interactions may increase or decrease the activity of VON-P Capsules when taken together with certain other medicines. VON-P Capsules may interact with the following medicines and salts:

- Alcohol
- Aspirin
- Cimetidine
- Corticosteroids

4.6. Pregnancy and lactation

Pregnancy:
There is no experience of use of this product in humans during pregnancy.
Congenital abnormalities have been reported in association with NSAID administration in man; however these are low in frequency and do not appear to follow any discernible pattern. In view of the known affects of NSAIDs on the foetal cardiovascular system (risk of closure of ductus arteriosus), use in the last trimester is contraindicated. The onset of labour may be delayed and duration increased with an increased bleeding tendency in both mother and child (see Section 4.3). NSAIDs should not be used during the first two trimesters of pregnancy or labour unless the potential benefit to the patient outweighs the potential risk to the foetus.

Epidemiological studies in human pregnancy have shown no ill effects due to paracetamol use at the recommended dosage.

Therefore if possible, the use of this product should be avoided in the first six months of pregnancy and contraindicated in the last three months of pregnancy (see Section 4.3).

Lactation:
Ibuprofen and its metabolites can pass in very small amounts (0.0008% of the maternal dose) into the breast milk. No harmful effects to infants are known.
Paracetamol is excreted in breast milk but not in a clinically significant amount. Available published data do not contraindicate breastfeeding.
Therefore it is not necessary to interrupt breastfeeding for short-term treatment with the recommended dose of this product.

4.7. Effects on ability to drive and use machines

Undesirable effects such as dizziness, drowsiness, fatigue and visual disturbances are possible after taking NSAIDs. If affected patients should not drive or operate machinery.

4.8. Undesirable effects

The following is an exhaustive list of side-effects that may occur for all the constituting molecules of VON-P Capsules. Some of these side-effects may be very rare or not found if the salt or molecule is in trace amounts. Not every side effect occurs in every person. Medicines that are approved for sale by governments are expected to be safe for the general population, although new or un-reported side effects may be found later. Please consult your doctor if you observe any of these side effects even in mild form:

- Abdominal pain
- Abnormal blood counts
- Abnormalities of blood cells
- Acute renal tubular necrosis

4.9. Overdose

Paracetamol

Liver damage is possible in adults who have taken 10 g (equivalent to 20 tablets) or more of paracetamol. Ingestion of 5 g (equivalent to 10 tablets) or more of paracetamol may lead to liver damage if the patient has one or more of the risk factors below:

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 alcohol in excess of recommended amounts.

c) Is likely to be glutathione depleted e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia

Symptoms

Symptoms of paracetamol overdose in the first 24 hours include pallor, nausea, vomiting, anorexia and abdominal pain. Liver damage may become apparent 12 to 48 hours after ingestion as liver function tests become abnormal. 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.

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.

Patients who present with serious hepatic dysfunction beyond 24 hours from ingestion should be managed in accordance with established guidelines.

Ibuprofen

Symptoms

Most patients who have ingested clinically important amounts of NSAIDs will develop no more than nausea, vomiting, epigastric pain, or more rarely diarrhoea. Tinnitus, headache and gastrointestinal bleeding are also possible. In more serious poisoning, toxicity is seen in the central nervous system, manifesting as drowsiness, occasionally excitation and disorientation or coma. Occasionally patients develop convulsions. In serious poisoning metabolic acidosis may occur and the prothrombin time / INR may be prolonged, probably due to interference with the actions of circulating clotting factors. Acute renal failure and liver damage may occur if there is a co-incident of dehydration. Exacerbation of asthma is possible in asthmatics.

Management

Management should be symptomatic and supportive and include the maintenance of a clear airway and monitoring of cardiac and vital signs until stable. Consider oral administration of activated charcoal if the patient presents within 1 hour of ingestion of a potentially toxic amount. If frequent or prolonged, convulsions should be treated with intravenous diazepam or lorazepam. Give bronchodilators for asthma.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group:

ATC code: M01AE51

5.1. Pharmacodynamic properties

The pharmacological actions of ibuprofen and paracetamol differ in their site and mode of action. These complementary modes of action are synergistic which results in greater antinociception and antipyresis than the single actives alone.

Ibuprofen is an NSAID that has demonstrated its efficacy in the common animal experimental inflammation models by inhibition of prostaglandin synthesis. Prostaglandins sensitise nociceptive afferent nerve terminals to mediators such as bradykinin. Ibuprofen therefore elicits an analgesic effect through peripheral inhibition of the cycloxygenase-2 (COX-2) isoenzyme with a subsequent reduction in sensitisation of nociceptive nerve terminals. Ibuprofen has also been shown to inhibit induced-leucocyte migration into inflamed areas. Ibuprofen has a pronounced action within the spinal cord due, in part, to the inhibition of COX. Ibuprofen's antipyretic effects are produced by the central inhibition of prostaglandins in the hypothalamus. Ibuprofen reversibly inhibits platelet aggregation. In humans, ibuprofen reduces inflammatory pain, swellings and fever.

Experimental data suggest that ibuprofen may inhibit the effect of low dose acetylsalicylic acid on platelets aggregation when they are dosed concomitantly. In one study, when a single dose of ibuprofen 400mg was taken within 8 h before or within 30 min after immediate release acetylsalicylic acid (81mg), a decreased effect of acetylsalicylic acid on the formation of thromboxane or platelet aggregation occurred. However, the limitations of these data and the uncertainties regarding extrapolation of ex vivo data to the clinical situation imply that no firm conclusions can be made for regular ibuprofen use, and no clinically relevant effect is considered to be likely for occasional ibuprofen use.

Paracetamol's exact mechanism of action is still not completely defined; however there is considerable evidence to support the hypothesis of a central antinociceptive effect. Various biochemical studies point to inhibition of central COX 2 activity. Paracetamol may also stimulate the activity of descending 5-hydroxytryptamine (serotonin) pathways that inhibit nociceptive signal transmission in the spinal cord. Evidence has shown that paracetamol is a very weak inhibitor of peripheral COX-1 and 2 isoenzymes.
This product is especially suitable for pain which requires stronger pain relief than ibuprofen 400 mg or paracetamol 1000 mg alone, and faster pain relief than ibuprofen.

Randomised, double-blind placebo-controlled studies were conducted with the combination using the acute pain model of post-operative dental pain. The studies show that:

- *This product provides more effective pain relief than paracetamol 1000 mg ($p<0.0001$).*
- *Duration of analgesia was significantly longer for this product (8.4 hours) compared to paracetamol 500 mg (4 hours, $p<0.0001$) or 1000 mg (5.2 hours, $p<0.0001$).*
- *The global evaluation of the study medication by the subjects showed high levels of satisfaction with 88.0% rating the product as 'good', 'very good' or 'excellent' in achieving pain relief. The fixed combination product performed significantly better than ibuprofen 200mg, paracetamol 500mg and 1000 mg ($p<0.001$ in all cases).*

  A one tablet dose of this product provides more effective pain relief than a combination of paracetamol 1000 mg / codeine phosphate 30 mg ($p=0.0001$) and was shown to be non-inferior to a combination of ibuprofen 400 mg / codeine phosphate 25.6 mg.

  This product has a fast onset of action with 'confirmed perceptible pain relief' achieved in a median of 15.6 minutes (1tablet dose) or 18.3 minutes (2 tablets dose), which is faster than for ibuprofen 200 mg (30.1 minutes, $p<0.001$), ibuprofen 400 mg (23.8 minutes, $p=0.0001$) and paracetamol 500 mg (23.7 minutes, $p=0.0001$). 'Meaningful pain relief' for this product was achieved in a median of 39.3 minutes (1 tablet dose) or 44.6 minutes (2 tablets dose), which was significantly faster than for ibuprofen 200 mg (80.0 minutes, $p<0.0001$), ibuprofen 400 mg (70.5 minutes, $p=0.0001$), paracetamol 500 mg (50.4 minutes, $p=0.001$) and paracetamol 1000 mg (45.6 minutes, $p<0.05$)

  Other randomised, double-blind placebo-controlled studies were conducted with the combination using the acute pain model of post-operative dental pain. The studies show that:

- This product provides more effective pain relief than paracetamol 1000 mg ($p<0.0001$) and ibuprofen 400 mg ($p< 0.05$).
- Duration of analgesia was significantly longer for this product (9.1 hours) compared to paracetamol 500 mg (4 hours) or 1000 mg (5.2 hours).
- The global evaluation of the study medication by the subjects showed high levels of satisfaction with 93.2% rating the product as 'good', 'very good' or 'excellent' in achieving pain relief. The fixed combination product performed significantly better than paracetamol 1000 mg ($p<0.0001$).

Another randomised, double-blind controlled clinical study was conducted with the product in the treatment of chronic knee pain. The study showed that:

- The product provides more effective pain relief than paracetamol 1000 mg in short term treatment ($p<0.01$) and long term treatment ($p<0.01$).
- The global evaluation of the product by the subjects showed high levels of satisfaction with 60.2% rating the product as 'good' or 'excellent' as a long term treatment for a painful knee. The product performed significantly better than paracetamol 1000 mg ($p<0.001$).

This product provides more effective pain relief than a combination of paracetamol 1000 mg / codeine phosphate 30 mg ($p<0.0001$), and a combination of ibuprofen 400 mg / codeine phosphate 25.6 mg ($p=0.0001$).

5.2 Pharmacokinetic properties

Ibuprofen is well absorbed from the gastrointestinal tract and is extensively bound to plasma proteins. Ibuprofen diffuses into the synovial fluid. Plasma levels of ibuprofen from this product are detected from 5 minutes with peak plasma concentrations achieved within 1-2 hours after ingestion on an empty stomach. When this product was taken with food peak ibuprofen plasma levels were lower and delayed by a median of 25 minutes, but overall extent of absorption was equivalent.

Ibuprofen is metabolised in the liver to two major metabolites with primary excretion via the kidneys, either as such or as major conjugates, together with a negligible amount of unchanged ibuprofen. Excretion by the kidney is both rapid and complete. The elimination half-life is approximately 2 hours.
In limited studies, ibuprofen appears in the breast milk in very low concentrations.

No significant differences in ibuprofen pharmacokinetic profile are observed in the elderly.
Paracetamol is readily absorbed from the gastrointestinal tract. Plasma protein binding is negligible at usual therapeutic concentrations, although this is dose-dependent. Plasma levels of paracetamol from this product are detected from 5 minutes with peak plasma concentrations occurring at 0.5-0.67 hours after ingestion on an empty stomach. When this product was taken with food peak paracetamol plasma levels were lower and delayed by a median of 55 minutes, but overall extent of absorption was equivalent.

Paracetamol is metabolised in the liver and excreted in the urine mainly as the glucuronide and sulphate conjugates, with about 10% as glutathione conjugates. Less than 5% is excreted as unchanged paracetamol. The elimination half-life is approximately 3 hours.

A minor hydroxylated metabolite, which is usually produced in very small amounts by mixed function oxidases in the liver and detoxified by conjugation with liver glutathione, may accumulate following paracetamol overdose and cause liver damage.

No significant differences in the paracetamol pharmacokinetic profile are observed in the elderly.
The bioavailability and pharmacokinetic profiles of ibuprofen and paracetamol taken as this product are not altered when taken in combination as a single or repeat dose.

This product is formulated using a technology which releases both Ibuprofen and Paracetamol simultaneously, so that the active ingredients deliver a combination effect.

5.3 Preclinical safety data

The toxicological safety profile of ibuprofen and paracetamol has been established in animal experiments and in humans from extensive clinical experience. There are no new preclinical data of relevance to the prescriber which are additional to the data already presented in this Summary of Product Characteristics.

6. PHARMACEUTICAL PARTICULARS

6.1. List of Excipients

Sodium Lauryl Sulphate
Sodium Benzoate
Starch
Talcum
Magnesium Stearate
Sodium Starch Glycollate

6.2 Incompatibilities

Not Known

6.3 Shelf life

36 Months

6.4 Special precautions for storage

Store in cool, dry and dark place.

6.5 Nature and contents of container

Aluminium PVC blister Pack

10 Capsules are packed in Aluminium PVC blister pack;

Pack size: 1 x 10 Capsules in one carton (10 capsules) along with packing leaflet.

6.6 Special precautions for disposal

No special requirements

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Brand Name : VON-P CAPSULES	
Generic Name : Ibuprofen, Paracetamol and Caffeine Capsules	

7.0 Manufacturer

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