Zott® P

℞ Zaltoprofen 80 mg and Paracetamol 325 mg Tablets

COMPOSITION

Each enteric coated tablet contains:

Zaltoprofen JP…….…….....80 mg

Paracetamol IP …….325mg

Excipients……..q.s.

Colours: Lake Tartrazine, Lake Sunset Yellow and Titanium Dioxide IP

PHARMACEUTICAL FORM

Enteric Coated Tablet

THERAPEUTIC INDICATION

For anti-inflammatory and analgesic activity in rheumatoid arthritis, osteoarthritis, low back pain, periarthritis of shoulder, cervicobrachial syndrome, postoperative, post trauma and post dental extraction

Carefully consider the potential benefits and risks of combination of Zaltoprofen and Paracetamol before deciding the use.

POSOLOGY AND METHOD OF ADMINISTRATION

The recommended adult oral dosage of ZOTT P (Zaltoprofen and Paracetamol) is one tablet three times daily.

CONTRAINDICATIONS

Zaltoprofen and Paracetamol is contraindicated in -

- Patients sensitive to Zaltoprofen and/or Paracetamol or to any of the excipients of the product
- Patients with Active peptic ulcer or GI bleeding or history of peptic ulcer disease or peptic ulcer due to chronic administration of non-steroidal ankle inflammatory drug
- Patients with severe blood abnormalities may worsen blood abnormalities.
- Patients with severe liver impairment may worsen liver damage.
- Patients with severe renal impairment may worsen renal impairment.
- Patients with severe heart failure or cardiac dysfunction may worsen “cardiac dysfunction.”
- Patients with ulcerative colitis and Crohn’s disease.
- Patients who have experienced asthma, urticaria, or other allergic type reactions after taking aspirin or other NSAIDs

SPECIAL WARNINGS & PRECAUTIONS FOR USE

Zaltoprofen

- Keep in mind that treatment with anti-inflammatory painkillers is symptomatic.
- When using this drug for chronic diseases (rheumatoid arthritis, osteoarthritis, etc.), consider the following considerations:
  - Periodic clinical examination (urine test, blood test, and liver function inspection, etc.) are performed in case of long-term administration. In addition, if an abnormality is recognized, the appropriate measures such as weight loss and the absence medicine are taken.
  - To consider other therapies other than drug therapy.
- When using this drug for acute diseases, consider the following matters:
  - Take into account the degree of acute inflammation, pain and fever.
  - Avoid long-term administration of the same drug in principle.
- Observe the condition of the patient sufficiently and keep the expression of side effects in mind.
- Because there is a possibility that an infectious disease may be inactivated, it is necessary to use the appropriate antibacterial agent in combination with the inflammation caused by infection, and carefully administer and observe sufficiently.
- It is desirable to avoid combination with other anti-inflammatory painkillers.
- Care should be given to the elderly with special attention to the expression of side effects and to minimize the use of the necessary minimum.

Paracetamol

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

Do not exceed the stated dose.

Patients should be advised to consult their doctor if their headaches become persistent.

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

Patients should be advised to consult a doctor if they suffer from non-serious arthritis and need to take painkillers every day.

If symptoms persist consult your doctor.

Keep out of the sight and reach of children.

USE IN SPECIAL POPULATIONS

Pregnancy and Lactation

The Zaltoprofen and Paracetamol should be used during pregnancy and lactation only after weighing the benefits and risks as suggested by the physician.

Zaltoprofen:

- A pregnant woman or a woman who may be pregnant should be administered only when the therapeutic benefits are judged to outweigh the risks. “The safety of the administration during pregnancy has not been established.”
- There is a report that temporary infertility has been observed in women who have been administered non-steroidal anti-inflammatory painkillers for a long period of time.
- Experiments administered to rats at the end of pregnancy, the vascular contraction of the fetus has been reported.
- It is preferable to avoid administering to a nurse, but to avoid breastfeeding when administered without necessity. Animal experiments (rats) have been reported to migrate in milk.

Paracetamol:

Epidemiological studies in human pregnancy have shown no ill effects due to paracetamol used in the recommended dosage, but patients should follow the advice of the doctor regarding its use. Paracetamol is excreted in breast milk but not in a clinically significant amount. Available published data do not contraindicate breast feeding.

Renal impairment-

The care is advised for the use of Zaltoprofen and Paracetamol in patients with renal impairment.

Zaltoprofen:

Zaltoprofen should be administered carefully to the patients with renal disorder or a history of “renal disorder may be exacerbated or recurred.”

Paracetamol:

Care is advised in the administration of paracetamol to patients with renal impairment.

Liver impairment-

Care is advised in patients with hepatic impairment

Zaltoprofen:

Zaltoprofen should be administered carefully to the patients with hepatopathy or a history of it “There is a danger of liver injury or recurrence.”

Paracetamol:

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

Elderly

The caution should be exercised in treating the elderly (65 years and older).

Zaltoprofen is a high plasma protein binding rate, and is mainly excreted from the kidney, in the elderly, it is often that the plasma albumin is reduced, renal function may also be lowered, because there is a possibility that the high blood concentration persists, while observing the state of the patient, such as gastrointestinal symptoms, Reduce the number of doses (for example, one tablet twice a day) or be administered carefully, such as a closed drug.

Pediatric Use

The safety and efficacy of Zaltoprofen and Paracetamol in children and adolescents aged below 18 years have not been established

DRUG INTERACTIONS

Zaltoprofen

Combined use caution (Be careful of concomitant use)

Quinolone antibacterials - Concomitant use of antibacterials with Zaltoprofen may trigger convulsion. The dose may have to be adjusted in such cases.

Coumarin anticoagulant agent- the dose may have to be adjusted as there may be intensification in the anticoagulant action.

Sulfonylurea antidiabetic agents - The dose may have to be adjusted as there may be an intensification in the hypoglycemic action.

Lithium - The dose of lithium may have to be adjusted as there may be intensification in the lithium action.

Methotrexate - Since there is a report that it will enhance the action of methotrexate, care should be taken to adjust the dose of methotrexate.

Paracetamol

The speed of absorption of paracetamol may be increased by metoclopramide or domperidone and absorption reduced by Cholestyramine. The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular daily use of paracetamol with increased risk of bleeding; occasional doses have no significant effect.

UNDESIRABLE EFFECTS

Zaltoprofen

Major side effects such as rash, skin irritation, stomach discomfort, stomachache, the digestive symptoms, such as heart pain, diarrhea, and heartburn, shock as a serious side effect, anaphylactic-like symptoms, acute renal failure, nephrotic syndrome, hepatic dysfunction, digestive crushing indemnity, small intestine / colon ulcer, hemorrhagic colitis, atherosclerosis, leukopenia, thrombocytopenia may occur. Also, as a serious side effect of drugs, other non-steroidal anti-inflammatory painkillers, skin mucosal ocular syndrome (Stevens-Johnson syndrome), toxic epidermal necrosis (Lyell syndrome), hemolytic anemia, aplastic anemia has been reported to appear.

Serious side effects (Frequency unknown)

- **Shock, anaphylactoid symptoms:** Shock, anaphylactoid-like symptoms may occur, so observe thoroughly, dyspnoea, blood pressure decrease, cold sweat, chills, rash, itching, flushing, facial edema, measles, etc. appear If so, discontinue administration and take appropriate measures.
- **Acute renal failure, nephrotic syndrome:** Acute renal failure, nephrotic syndrome and other kidney problems may occur, so observe thoroughly, increase BUN • blood creatinine rise, oliguria, edema, proteinuria, low protein If abnormalities such as hematoses are observed, discontinue administration and take appropriate measures.
- **Liver function disorder:** yellow pox, AST (GOT) elevation, ALT (GPT) elevation, Al - P elevation, γ - GTP elevation may occur, so observe thoroughly and if abnormality is found take appropriate measures, such as discontinue administration.
- **Peptic ulcer cancer, small intestine / colon ulcer cancer, hemorrhagic colitis:** digestive ulcer and small intestine / colon ulcer (which may accompany bleeding and perforation), hemorrhagic colitis may appear, observe adequately, if abnormalities are observed discontinue administration and take appropriate measures.
- **Ableglia, leukocytopenia, thrombocytopenia:** non granulocytosis, leucopenia, thrombocytopenia may occur, so observe thoroughly, regular blood tests and abnormalities are observed. If so, discontinue administration and take appropriate measures.

  Serious side effects (in case of drugs) “Frequency unknown”
- **Skin mucosa ocular syndrome, toxic epidermal necrosis:** It is reported that other non-steroidal anti-inflammatory analgesics, skin mucosa ocular syndrome (Stevens-Johnson syndrome), toxic epidermal necrosis (Lyell syndrome) appears. Therefore, in such a case, discontinue administration and take appropriate measures.
- **Hemolytic anemia, aplastic anemia:** Since it is reported that hemolytic anemia and aplastic anemia appear in other non-steroidal anti-inflammatory analgesics, observe thoroughly by conducting blood tests, etc. If abnormality is observed, discontinue the administration immediately and take appropriate measures.

	Frequency Unknown
Digestive organ	Stomach discomfort, stomach pain, recital, heart bulk pain, diarrhea, heavy stomach, heartburn, dry mouth (thirst)
Mental nervous system	Drowsiness, dizziness, headaches, numbness (feeling)
Hypersensitivity	Photosensitivity, rashes, eczema
Blood	Hemoglobin decrease, decrease in hematocrit value, red blood cell reduction, eosinophilia, increase in blood platelets, increase in leukocytes
Liver	ALT (GPT) increase, AST (GOT) increase, AI 1 P increase, γ 1 GTP increase
Kidney	Increased BUN, elevated blood creatinine, hematuria
Other	Hot flashes, frequent urination, edema, malaise, urination pain, urination disorder, fever

If such symptoms appear, discontinue the administration.

Paracetamol

Adverse events of paracetamol from historical clinical trial data are both infrequent and from small patient exposure. Accordingly, events reported from extensive post-marketing experience at therapeutic/labelled dose and considered attributable are tabulated below by system class. Due to limited clinical trial data, the frequency of these adverse events is not known (cannot be estimated from available data), but post-marketing experience indicates that adverse reactions to paracetamol are rare and serious reactions are very rare.

Post marketing data

Body System Undesirable effect: Blood and lymphatic system disorders, Thrombocytopenia, Agranulocytosis, Immune system disorders, Anaphylaxis, Cutaneous hypersensitivity reactions including skin rashes, Angioedema and Stevens Johnson syndrome/toxic epidermal necrolysis, Respiratory, thoracic and mediastinal disorders, Bronchospasm*, Hepatobiliary disorders, Hepatic dysfunction

* There have been cases of bronchospasm with paracetamol, but these are more likely in asthmatics sensitive to aspirin or other NSAIDs.

If serious adverse reactions occur, ZOTT P Tablets should be discontinued.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Kindly report any suspected adverse reactions to pharmavigil@jbcpl.com

OVERDOSE

There is no experience of overdose with Zaltoprofen and Paracetamol. Signs and symptoms of overdose are expected to be in line with exaggerated pharmacological effects of individual ingredient.

Zaltoprofen:

No human data available on the consequences of Zaltoprofen overdosage. The therapeutic measures to be taken are: absorption should be prevented, as soon as possible after overdosage by means of gastric lavage and treatment with activated charcoal; supportive and systematic treatment should be given for complications such as hypotension, renal failure, convulsion, gastrointestinal irritation and respiratory depression, specific therapies such as forced diuresis, dialysis or haemoperfusion are probably of no help in eliminating NSAIDs due to their high rate of protein binding and extensive metabolism.

Paracetamol

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

Risk Factors

If the patient

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

Or

b) Regularly consumes ethanol in excess of recommended amounts.

Or

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

Symptoms

Symptoms of paracetamol overdosage in the first 24 hours are pallor, nausea, vomiting, anorexia and abdominal pain. Liver damage may become apparent 12 to 48 hours after ingestion. Abnormalities of glucose metabolism and metabolic acidosis may occur. In severe poisoning, hepatic failure may progress to encephalopathy, haemorrhage, hypoglycaemia, cerebral oedema, and death. Acute renal failure with acute tubular necrosis, strongly suggested by loin pain, haematuria and proteinuria, may develop even in the absence of severe liver damage. Cardiac arrhythmias and pancreatitis have been reported.

Management

Immediate treatment is essential in the management of paracetamol overdose. Despite a lack of significant early symptoms, patients should be referred to hospital urgently for immediate medical attention. Symptoms may be limited to nausea or vomiting and may not reflect the severity of overdose or the risk of organ damage. Management should be in accordance with established treatment guidelines, see BNF overdose section.

Treatment with activated charcoal should be considered if the overdose has been taken within 1 hour. Plasma paracetamol concentration should be measured at 4 hours or later after ingestion (earlier concentrations are unreliable).

Treatment with N-acetylcysteine may be used up to 24 hours after ingestion of paracetamol however; the maximum protective effect is obtained up to 8 hours post ingestion.

If required the patient should be given intravenous-N-acetylcysteine, in line with the established dosage schedule. If vomiting is not a problem, oral methionine may be a suitable alternative for remote areas, outside hospital.

Management of patients who present with serious hepatic dysfunction beyond 24 hours from ingestion should be discussed with the NPIS or a liver unit.

CLINICAL PHARMACOLOGY

Pharmacodynamic Properties

Zaltoprofen

Zaltoprofen is (±)-2-(10,11-dihydro-10-oxodibenzo [b, f] thiepin-2-yl) propionic acid, belongs to the therapeutic class of nonsteroidal anti-inflammatory drugs (NSAIDs) that exhibits anti-inflammatory, analgesic on inflammatory pain and antipyretic activities.

Zaltoprofen is a COX-2 preferential inhibitor. The main mechanism of Zaltoprofen is prostaglandin biosynthesis inhibitory action due to the COX inhibition in the arachidonic acid metabolism system. Besides this, membrane stabilizing action such as leukocyte migration inhibitory action and lysosomal enzyme inhibitory action are also observed with Zaltoprofen. Experimental studies have shown that Prostaglandin biosynthesis inhibitory action in the stomach tissue is weaker with Zaltoprofen than in case of indomethacin.

Zaltoprofen possesses novel anti-nociceptive mechanism by inhibiting B2-type bradykinin (BK) receptor function in nerve endings and selectively inhibiting PGE2 production at inflammatory sites and exhibits a powerful anti-inflammatory effect with a good safety margin. and stronger inhibitory effect on BK-nociception than other NSAIDs.

Paracetamol

Analgesic – 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.

Antipyretic – paracetamol probably produces antipyresis by acting centrally on the hypothalamic heat-regulation centre to produce peripheral vasodilation resulting in increased blood flow through the skin, sweating and heat loss. The central action probably involves inhibition of prostaglandin synthesis in the hypothalamus.

Pharmacokinetic Properties

Zaltoprofen

After oral administration, Zaltoprofen is well absorbed (82%) in the GIT. About 98% of the administered drug is bound to plasma proteins. After oral administration, 62% of the dose is excreted as conjugate in the urine and only 3% is excreted as unchanged compound by this route. No systemic accumulation has been reported. Zaltoprofen has biological half-life of 2.8 hr.

The Zaltoprofen is predominantly metabolized by CYP2C9 and UGT2B7 in liver. Zaltoprofen is also biotransformed to S-oxide Zaltoprofen (M-2), 10-hydroxy Zaltoprofen (M-3) and S-oxide-10-hydroxy-Zaltoprofen (M-5) in humans, and conjugate of M-2 and M-3 are excreted in urine, although urinary level of each of these metabolites account for less than 10% of the dose. There is a biphasic reduction in plasma concentration. ($T_{1/2\alpha}$ around 0.9hours and $T_{1/2\beta}$ around 9 hours).

Paracetamol

Paracetamol is rapidly and almost completely absorbed from the gastrointestinal tract. The concentration in plasma reaches a peak in 30 to 60 minutes and the plasma half-life is 1 - 4 hours after therapeutic doses. Paracetamol is relatively uniformly distributed throughout most body fluids. Binding of the drug to plasma proteins is variable; 20 to 30% may be bound at the concentrations encountered during acute intoxication. Following therapeutic doses 90 - 100% of the drug may be recovered in the urine within the first day. However, practically no paracetamol is excreted unchanged and the bulk is excreted after hepatic conjugation.

INCOMPATIBILITIES

None known.

PACKAGING INFORMATION

Blister of 4 Tablets and 10 Tablets.

STORAGE AND HANDLING INSTRUCTIONS

Store in a cool, dry & dark place. Keep out of reach of children.

Marketed by & ® Regd. Trade Mark of :
J. B. CHEMICALS & PHARMACEUTICALS LTD.
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Note: This prescribing information is applicable for India Market only.