Summary of Product Characteristics
UPRONE™

1. **Name of the medicinal product:**
   UPRONE™

2. **Qualitative and Quantitative composition:**
   Each Vial Contains:

   Omeprazole Sodium BP eq. to Omeprazole 40 mg

3. **Pharmaceutical form:**
   Sterile powder for injection

4. **Clinical Particulars:**

4.1 Therapeutic indication:

Omeprazole for intravenous use is indicated as an alternative to oral therapy for the following indications in adults:

Treatment of duodenal, gastric ulcers, NSAID associated ulcers, reflux oesophagitis, symptomatic gastro-Oesophageal reflux disease, Zollinger-Ellison syndrome and related relapses.

In combination with appropriate antibiotics, Helicobacter pylori (H. pylori) eradication in peptic ulcer disease

4.2 Posology and Method of Administration:

In patients where the use of oral medicinal products is inappropriate, Omeprazole IV 40 mg once daily is recommended OR as directed by the physician

After reconstitution the injection should be given slowly over a period of at least 2.5 minutes at a maximum rate of 4 ml per minute.

Injection:

For IV injection, reconstitute one sterile single dose vial of Omeprazole with 10 ml of sterile Solution for Injection to make 10 ml solution with 4 mg/ml of Omeprazole approximately.

The reconstituted solution should not be used if it contains visible particulate material

Infusion:

For IV infusion, reconstitute one sterile single dose vial of Omeprazole Injection with 10 ml of sterile Solution for Injection to make 10 ml solution containing 4 mg/ml of Omeprazole approximately. Subsequently add 10 ml of reconstituted solution containing 4 mg/ml of Omeprazole approximately, to 90 ml of Sodium Chloride solution BP(containing 0.9 % w/v Sodium Chloride) or 90 ml of Dextrose Injection (containing 5 % w/v of Dextrose) or 90 ml Mannitol BP(containing 5 % w/v of Mannitol) to make sure 100 ml solution of 0.4 mg/ml of Omeprazole approximately. No other solution should be used for infusion. The resultant infusion should be given intravenously over a period of 23 – 30 minutes. The prepared infusion solution should be used within 3 hours of preparation and any unused portion should be discarded.

Impaired renal function: Dose adjustment is not needed in patients with impaired renal function.

Impaired hepatic function: In patients with impaired hepatic function a daily dose of 10 - 20 mg may be sufficient.

Elderly (> 65 years old): Dose adjustment is not needed in the elderly.

Paediatric patients: There is limited experience with Omeprazole for intravenous use in children.

4.3 Contradictions:

Contraindicated in patients with hypersensitivity to omeprazole, substituted benzimidazoles, nelfinavir or to any of the excipients.

4.4 Special warnings and precautions for use:

Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as Salmonella and Campylobacter.

As in all long-term treatments, especially when exceeding a treatment period of 1 year, patients should be kept under regular surveillance

4.5 Interaction with other medicinal products and other forms of interaction

The decreased intragastric acidity during treatment with omeprazole might increase or decrease the absorption of active substances with a gastric pH dependent absorption such as nelfinavir,

atazanavir, digoxin, clopidogrel The absorption of posaconazole, erlotinib, ketoconazol and itraconazol is significantly reduced and thus clinical efficacy may be impaired. Omeprazole is a moderate inhibitor of CYP2C19, the major omeprazole metabolising enzyme. Thus, the metabolism of concomitant active substances also metabolised by CYP2C19, may be decreased and the systemic exposure to these substances increased. Examples of such drugs are R-warfarin and other vitamin K antagonists, cilostazol, diazepam and phenytoin.

Unknown mechanism

Concomitant administration of omeprazole with saquinavir/ritonavir, tacrolimus resulted in increased plasma levels for saquinavir and tacrolimus

Inhibitors of CYP2C19 and/or CYP3A4

Since omeprazole is metabolised by CYP2C19 and CYP3A4, active substances known to inhibit CYP2C19 or CYP3A4 (such as clarithromycin and voriconazole) may lead to increased omeprazole serum levels by decreasing omeprazole's rate of metabolism.

Active substances known to induce CYP2C19 or CYP3A4 or both (such as rifampicin and St John's wort) may lead to decreased omeprazole serum levels by increasing omeprazole's rate of metabolism.

4.6 Pregnancy and lactation:

Results from three prospective epidemiological studies (more than 1000 exposed outcomes) indicate no adverse effects of omeprazole on pregnancy or on the health of the foetus/newborn child. Omeprazole can be used during pregnancy.

Omeprazole is excreted in breast milk but is not likely to influence the child when therapeutic doses are used.

4.7 **Effects on ability to drive and use of machines:**

Uprone is not likely to affect the ability to drive or use machines. Adverse drug reactions such as dizziness and visual disturbances may occur. If affected, patients should not drive or operate machinery.

4.8 Undesirable effects:

The most common side effects are headache, abdominal pain, constipation, diarrhoea,

flatulence and nausea/vomiting. Rare adverse effects observed are leukopenia, thrombocytopenia, hypersensitivity reactions e.g. fever, angioedema and anaphylactic reaction/shock, hypernatremia, agitation, confusion, depression, taste disturbance, blurred vision, bronchospasm, dry mouth, stomatitis, gastrointestinal Candidiasis, hepatitis with or without jaundice, alopecia, photosensitivity, arthralgia, myalgia, interstitial nephritis and increased sweating Very rare reactions observed were agranulocytosis, pancytopenia, hypomagnesaemia, aggression, hallucinations, hepatic failure, encephalopathy in patients with pre-existing liver disease, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), muscular weakness, gynaecomastia

4.9 Overdose:

There is limited information available on the effects of overdoses of omeprazole in humans. In the literature, doses of up to 560 mg have been described, and occasional reports have been received when single oral doses have reached up to 2,400 mg omeprazole (120 times the usual recommended clinical dose). Nausea, vomiting, dizziness, abdominal pain, diarrhoea and headache have been reported. Also apathy, depression and confusion have been described in single cases. The symptoms described have been transient, and no serious outcome has been reported. The rate of elimination was unchanged (first order kinetics) with increased doses. Treatment, if needed, is symptomatic. Intravenous doses of up to 270 mg on a single day and up to 650 mg over a three-day period have been given in clinical trials without any dose-related adverse reactions.

5. Pharmacological properties

5.1 Pharmacodynamic properties:

Pharmacodynamic properties:

Mechanism of action: Omeprazole, Proton pump inhibitors reduces gastric acid secretion through a highly targeted mechanism of action. It is a specific inhibitor of the acid pump in the parietal cell. It is rapidly acting and provides control through reversible inhibition of gastric acid secretion with once daily dosing. Omeprazole is a weak base and is concentrated and converted to the active form in the highly acidic environment of the intracellular canaliculi within the

parietal cell, where it inhibits the enzyme H+,K+-ATPase - the acid pump. This effect on the final step of the gastric acid formation process is dose-dependent and provides for highly effective inhibition of both basal acid secretion and stimulated acid secretion, irrespective of stimulus.
Effect on gastric acid secretion: Intravenous omeprazole produces a dose dependent inhibition of gastric acid secretion in humans. In order to immediately achieve a similar reduction of intragastric acidity as after repeated dosing with 20 mg orally, a first dose of 40 mg intravenously is recommended. This results in an immediate decrease in intragastric acidity and a mean decrease over 24 hours of approximately 90% for both iv injection and iv infusion. The inhibition of acid secretion is related to the area under the plasma concentration-time curve (AUC) of omeprazole and not to the actual plasma concentration at a given time. No tachyphylaxis has been observed during treatment with omeprazole.

5.2 Pharmacokinetic properties

Distribution: The apparent volume of distribution in healthy subjects is approximately 0.3 l/kg body weight. Omeprazole is 97% plasma protein bound.

Metabolism: Omeprazole is completely metabolised by the cytochrome P450 system (CYP). The major part of its metabolism is dependent on the polymorphically expressed CYP2C19, responsible for the formation of hydroxyomeprazole, the major metabolite in plasma. The remaining part is dependent on another specific isoform, CYP3A4, responsible for the formation of omeprazole sulphone. As a consequence of high affinity of omeprazole to CYP2C19, there is a potential for competitive inhibition and metabolic drug-drug interactions with other substrates for CYP2C19. However, due to low affinity to CYP3A4, omeprazole has no potential to inhibit the metabolism of other CYP3A4 substrates. In addition, omeprazole lacks an inhibitory effect on the main CYP enzymes. Approximately 3% of the Caucasian population and 15-20% of Asian populations lack a functional CYP2C19 enzyme and are called poor metabolisers. In such individuals the metabolism of omeprazole is probably mainly catalysed by CYP3A4.
After repeated once-daily administration of 20 mg omeprazole, the mean AUC was 5 to 10 times higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean peak plasma concentrations were also higher, by 3 to 5 times. These

findings have no implications for the posology of omeprazole.

Excretion: Total plasma clearance is about 30–40 l/h after a single dose. The plasma elimination half-life of omeprazole is usually shorter than one hour both after single and repeated once-daily dosing. Omeprazole is completely eliminated from plasma between doses. Almost 80% of a dose of omeprazole is excreted as metabolites in the urine, the remainder in the faeces, primarily originating from bile secretion. The AUC of omeprazole increases with repeated administration due to a decrease of systemic clearance probably caused by an inhibition of the CYP2C19 enzyme by omeprazole and/or its metabolites (e.g. the sulphone). No metabolite has been found to have any effect on gastric acid secretion.

Special populations:

Impaired hepatic function: The metabolism of omeprazole in patients with liver dysfunction is impaired, resulting in an increased AUC. Omeprazole has not shown any tendency to accumulate with once-daily dosing.

Impaired renal function: The pharmacokinetics of omeprazole, including systemic bioavailability and elimination rate, are unchanged in patients with reduced renal function.

Elderly: The metabolism rate of omeprazole is somewhat reduced in elderly subjects (75-79 years of age).

5.3 Preclinical safety data:

Gastric ECL-cell hyperplasia and carcinoids, have been observed in life-long studies in rats treated with omeprazole. These changes are the result of sustained hypergastrinaemia secondary to acid inhibition. Similar findings have been made after treatment with H2-receptor antagonists, proton pump inhibitors and after partial fundectomy. Thus, these changes are not from a direct effect of any individual active substance.

6. Pharmaceutical particulars

6.1 List of excipients:

Diluent used for reconstitution- 10 ml Sodium Chloride Injection BP 0.9% w/v.

6.2 Incompatibilities:

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products except provided diluent for reconstitution.

6.3 Shelf life:

Unopened packs: 2 years.

Reconstituted solution:

From a microbiological point of view, the product should be used immediately unless it has been reconstituted under controlled and validated aseptic conditions.

6.4 Special precautions for storage:

Store in a dry place, below 30°C. Protected from light.

Do not use, if any particle, leakage or breakage is found.

6.5 Nature and contents of container:

Each Combipack contains one vial of Omeprazole for injection and 10 ml of SodiumChloride injection BP in a carton along with leaflet

7. Marketing Authorization Holder

BLISS GVS PHARMA LTD.

102, Hyde Park, Saki Vihar Road, Andheri (E), Mumbai - 400 072, INDIA.