SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDİCİNAL PRODUCT

OMEPREFUL 40 mg powder and solvent for solution for IV injection
Sterile

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:
Each package contains 1 vial containing lyophilized omeprazole and 1 ampoule containing solvent. Each vial contains 42.6 mg of omeprazole sodium, equivalent to 40 mg of omeprazole.

Excipients:
Sodium hydroxide …… .. y.m.

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Lyophilized powder and solvent to prepare the solution for injection.
In a type I colorless glass vial, a white or almost white lyophilized powder.

4. CLİNİCAL PARTİCULARS

4.1 Therapeutic indications

OMEPREFUL,

- Treatment of duodenal ulcer,
- Prevention of relapse of duodenal ulcer,
- Treatment of gastric ulcer,
- Prevention of relapse of stomach ulcers,
- Eradication of peptic ulcer with the combination of appropriate antibiotics and Helicobacter pylori (H. pylori),
- Treatment of NSAID-associated gastric and duodenal ulcers
- Prevention of NSAID-associated gastric and duodenal ulcers in patients at risk
- Treatment of reflux oesophagitis,
- Long-term management of patients with healed reflux
- Treatment of symptomatic gastro-oesophageal reflux disease,
- Treatment of Zollinger-Ellison syndrome

4.2 Posology and method of administration

Posology / frequency and duration of application:
Alternative to oral therapy
Patients who cannot be treated orally can be treated with 40 mg of omeprazole per day intravenously.

Zollinger-Ellison syndrome:
The dose should be adjusted according to the patient. The recommended dose is initially 60 mg per day, and more frequent and higher doses may be required. If the dose exceeds 60 mg, the dose should be divided and administered twice a day.

Method of administration
I.V. injection:
OMEPREFUL should be injected slowly intravenously. OMEPREFUL should not be added to

solutions for infusion. After the preparation of the solution, the injection should be carried out in a minimum of 2.5 minutes, as to be a maximum of 4 ml per minute. The solution should be applied within a maximum of 4 hours after preparation. See Section 6.6 for instructions on diluting the product prior to application.

Additional information on special populations:
Renal failure
Dose adjustment is not needed in patients with impaired renal function (see section 5.2).

Hepatic failure
In patients with impaired hepatic function a daily dose of 10-20 mg may be sufficient (see section 5.2).

Paediatric population
There is limited experience on intravenous use in children.

Geriatric population
Dose adjustment is not needed in the elderly patients aged 65 years or older (see section 5.2).

4.3 Contraindications
OMEPREFUL; should not be used in cases with hypersensitivity to omeprazole substituted benzimidazoles and other components in its content.

Omepreful, like other proton pump inhibitors (PPIs) should not be used concomitantly with nelfinavir (see section 4.5).

4.4 Special warnings and precautions for use
In the presence of any alarm symptoms (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melena) and when gastric ulcer is suspected or present, treastment should be started without excluding malignancy possiblity as it may alleviate symptoms and delay diagnosis.

Co-administration of omeprazol with atazanavir is not recommended (see section 4.5). If the combination of atazanavir with a proton pump inhibitor is inevitable, close clinical monitoring (e.g virus load) is recommended in combination of the dose of atazanavir up to 400 mg with 100 mg of ritonavir and omeprazole dose should not exceed 20 mg.

Omeprazole, as all acid-blocking medicinal products, may reduce the absorption of vitamin B12(cyanocobalamin) due to hypo- or achlorhydria. This should be considered in patients with reduced body reserves or risk factors due to reduced vitamin B12 absorption on long-term therapy.

Omeprazole is a CYP2C19 inhibitor. When starting or ending treatment with omeprazole, the potential for interactions with medicinal products metabolised through CYP2C19 should be considered. An interaction is observed between clopidogrel and omeprazole (see section 4.5). The clinical relevance of this interaction is uncertain. As a precaution, concomitant use of omeprazole and clopidogrel should be avoided.

Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as Salmonella and Campylobacter (see section 5.1).

Bone fracture:
Several published observational studies suggest that treatment of proton pump inhibitor (PPI) may be associated with an increased risk of fracture due to osteoporosis in the hip, wrist, or spine. The risk of fracture increased in patients receiving high doses defined as multiple daily doses and long-term PPI treatment (one year or more). Patients should receive the lowest dose and the shortest duration of PPI treatment for their condition.

Hypomagnesemia:
Symptomatic and asymptomatic hypomagnesemia have rarely been reported in patients treated with PPI for at least 3 months and in most cases after one year of treatment. Serious adverse events include tetany, arrhythmias and seizures. Hypomagnesemia treatment in most patients requires magnesium replacement and discontinuation of PPI therapy. For patients who are expected to receive treatment for a long period of time or who receive PPIs with drugs such as digoxin or drugs that may cause hypomagnesemia (eg diuretics), healthcare professionals may periodically monitor magnesium levels before and after starting PPI therapy.

Interactions with reviews for neuroendocrine tumors:
Serum chromogranin A (CgA) levels are increased secondary to drug-induced reductions in gastric acid levels. Increased CgA levels may lead to false positive results in diagnostic examinations for neuroendocrine tumors. Practitioners should temporarily discontinue PPI treatment before evaluating their CgA levels and repeat the test if initial CgA levels are high. If serial tests are performed (eg for monitoring), the tests should be performed in the same laboratory as the reference intervals between the tests may vary.

In particular, patients who have been treated for more than one year should be monitored regularly.

This medicinal product contains less than 1 mmol (23 mg) of sodium per ml; that is, it does not actually contain sodium.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of omeprazole on the pharmacokinetics of other active substances:

Medicinal products with pH dependent absorption:
The decreased intragastric acidity during treatment with omeprazole might increase or decrease the absorption of medicinal products with a gastric pH dependent absorption.

Nelfinavir, atazanavir:
The plasma levels of nelfinavir and atazanavir are decreased in case of co-administration with omeprazole.

Concomitant administration of omeprazole with nelfinavir is contraindicated (see section 4.3). Co-administration of omeprazole (40 mg once daily) reduced mean nelfinavir exposure by 40% and the mean exposure of the pharmacologically active metabolite M8 was reduced by 75-90%. The interaction may also involve CYP2C19 inhibition.

Concomitant administration of omeprazole with atazanavir is not recommended (see section 4.4). Co-administration of omeprazole (40 mg once a day) and atazanavir 300 mg / ritonavir

100 mg in healthy volunteers led to a 75% reduction in atazanavir exposure. Increasing the atazanavir dose to 400 mg did not compensate for the impact of omeprazole on atazanavir exposure. The co-administration of omeprazole (20 mg once daily) with atazanavir 400 mg/ritonavir 100 mg to healthy volunteers resulted in a decrease of approximately 30% in the atazanavir exposure as compared to atazanavir 300 mg/ritonavir 100 mg once daily.

Digoksin:
Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10%. Digoxin toxicity has been rarely reported. However caution should be given when omeprazole is administered at high doses in elderly patients. Afterwards, therapeutic drug monitoring of digoxin should be determined.

Clopidogrel:
Results of studies with healthy volunteers have shown that there is pharmacokinetics (PK) / pharmacodynamic (PD) interaction between clopidogrel (300 mg loading dose / 75 mg daily maintenance dose) and omeprazole (80 mg once daily).The exposure to the active metabolite of clopidogrel was decreased by 46% on average and inhibition of platelet aggregation 16% on average when clopidogrel and omeprazole were administered together.

Both observational and clinical studies have reported unclear data on the clinical implications of this PK / PD interaction for significant cardiovascular events. As a precaution, simultaneous use of omeprazole and clopidogrel should be avoided (see section 4.4).

Other medical products:
The absorption of posaconazole, erlotinib, ketoconazol and itraconazol is significantly reduced and thus clinical efficacy may be impaired. For posaconazol and erlotinib concomitant use should be avoided.

Medical products metabolised by CYP2C19:
Omeprazole inhibits CYP2C19 which is the major omeprazole metabolizing enzyme, moderately. Therefore, it can slow the metabolism of other drugs such as diazepam, phenytoin, warfarin (R-warfarin) and other vitamin K antagonists and cilostazol which are metabolized through the enzyme CYP2C19.

Cilostazol:
In a cross-over study where the Omeprazole was administered in doses of 40 mg to healthy subjects, Cmax and AUC for cilostazol was increased by 18% and 26% respectively, and one of its active metabolites by 29% and 69% respectively.

Phenytoin
Monitoring phenytoin plasma concentration is recommended during the first two weeks after initiating omeprazole treatment and, if a phenytoin dose adjustment is made, monitoring and a further dose adjustment should be performed upon ending omeprazole treatment.

<u>Unknown mechanism</u>
Saquinavir:
Concomitant administration of omeprazole with saquinavir/ritonavir resulted in increased plasma levels up to approximately 70% for saquinavir associated with good tolerability in HIV-infected patients.

Tacrolimus:
If omeprazole and tacrolimus are used together, an increase in plasma level of tacrolimus has been reported. Supported impression of tacrolimus concentrations, including renal function (creatinine clearance), should be carried out and, if necessary, tacrolimus dose adjusted.

Methotrexate:
In some patients, methotrexate levels have been reported to be increased when given with proton pump inhibitors. In the application of high-dose methotrexate, omeprazole administration may need to be temporarily discontinued.

Effects of other medications on the pharmacokinetics of omeprazole
Inhibitors of CYP2C19 and/or CYP3A4:
Since omeprazole is metabolised by CYP2C19 and CYP3A4, active substances known to inhibit CYP2C19 or CYP3A4 or both such as clarithromycin and voriconazole may lead to increase omeprazole serum levels by decreasing omeprazole's rate of metabolism. Concomitant voriconazole treatment resulted in more than doubling of the omeprazole exposure. As high doses of omeprazole have been well-tolerated adjustment of the omeprazole dose is not generally required when it is used temprorarily. However, dose adjustment should be considered in patients with severe hepatic impairment and if long-term treatment is indicated.

Inducers of CYP2C19 and/or CYP3A4:
The medications known to induce CYP2C19 or CYP3A4 or both such as rifampicin may lead to decrease omeprazole serum levels by increasing omeprazole's rate of metabolism.

Additional information about special populations
Pediatric population:
There is insufficient data to recommend pediatric use of omeprazole.

4.6 Pregnancy and lactation

General recommendation
Pregnancy Category: C

Women with childbearing potential / Contraception
There is insufficient data on the effects of reproductive ability on women with childbearing potential. Interaction between omeprazole and birth control pills was not reported.

Pregnancy
Animal studies are insufficient in terms of pregnancy and/or embryonal/fetal development and/or effects on childbirth and/or postpartum development (see section 5.3).
The potential risk for humans is unknown.

Three prospective epidemiological studies (including results from more than 1000 applications) indicate that omeprazole has no adverse effects on pregnant women and on the fetus or neonatal health.

OMEPREFUL should only be used if the benefits to the mother are above the potential risks for the fetus.

Lactation
Omeprazole passes into breast milk, but it is not expected to have an effect on the child when used in therapeutic doses. It is more appropriate not to be used during lactation.

Fertility
There is no study on the effect on fertility.

4.7 Effects on ability to drive and use machines
OMEPREFUL is not likely to affect the ability to drive or use machines. Adverse reactions such as dizziness and visual disturbances may occur (see section 4.8). The patients who are affected by these adverse effect, should not drive or use machines.

4.8 Undesirable effects
The most common adverse effects (1-10% of patients) are headache, abdominal pain, constipation, diarrhoea, flatulence and nausea/vomiting.

The following events have been reported as adverse effects in clinical studies and after marketing. None of these were dose related.

The frequency ratings of the undesirable effects listed below according to the system organ class are defined as follows:

Very common (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1,000 to <1/100), Rare (≥1/10,000 to <1/1,000), Very rare (<1/10,000), Not known (cannot be estimated from the available data).

Blood and lymphatic system disorders
Rare: Leukopenia, thrombocytopenia
Very rare: Agranulocytosis, pancytopenia

Immune system disorders
Rare: Hypersensitivity reactions e.g. fever, angioedema and anaphylactic reaction/shock

Metabolism and nutrition disorders
Rare: Hyponatraemia
Not known: Hypomagnesemia; severe hypomagnesemia may cause hypocalcemia.

Psychiatric disorders
Uncommon: Insomnia
Rare: Agitation, confusion, depression
Very rare: Aggression, hallucinations

Nervous system disorders
Common: Headache
Uncommon: Dizziness, paraesthesia, somnolence
Rare: Taste disturbance

Eye disorders
Rare: Blurred vision

Ear and labyrinth disorders
Uncommon: Vertigo

Respiratory, thoracic and mediastinal disorders
Rare: Bronchospasm

Gastrointestinal disorders
Common: Abdominal pain, constipation, diarrhoea, flatulence, nausea/vomiting, fundic gland polyps (benign)
Rare: Dry mouth, stomatitis, gastrointestinal candidiasis
Not known: Microscopic colitis

Hepatobiliary disorders
Uncommon: Increased liver enzymes
Rare: Hepatitis with or without jaundice
Very rare: Hepatic failure, encephalopathy in patients with pre-existing liver disease

Skin and subcutaneous tissue disorders
Uncommon: Dermatitis, pruritus, rash, urticaria
Rare: Alopecia, photosensitivity
Very rare: Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN)

Musculoskeletal disorders, connective tissue and bone diseases
Uncommon: Fracture of the hip, wrist or spine
Rare: Arthralgia, myalgia
Very rare: Muscular weakness

Renal and urinary disorders
Very rare: Interstitial nephritis

Reproductive system and breast disorders
Very rare: Gynaecomastia

General disorders and administration site conditions
Uncommon: Malaise, peripheral oedema
Rare: Increased sweating

Irreversible visual impairments have been reported in patients with severe disease, isolated cases, especially after intravenous treatment of high doses of omeprazole. However, a causal relationship between these symptoms and omeprazole treatment has not been established.

4.9 Overdose and therapy

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Proton pump inhibitors
ATC code: A02B C01

Mechanism of action:
Omeprazole, a racemic mixture of two enantiomers reduces gastric acid secretion through a highly targeted mechanism of action. It is a specific inhibitor of the acid pump in the parietal cell. Its effect on acid secretion is rapid and reversibly inhibits gastric acid secretion by single-dose treatment per day.
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.

All pharmacodynamic effects observed can be explained by the effect of omeprazole on acid secretion.

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.

Effect on *Helicobacter pylori*:
Helicobacter pylori is associated with peptic ulcer disease, including duodenal and gastric ulcer disease. H. pylori is a major factor in the development of gastritis. H. pylori together with gastric acid are major factors in the development of peptic ulcer disease. H. pylori is a major factor in the development of atrophic gastritis which is associated with an increased risk of developing gastric cancer.

Eradication of H. pylori with omeprazole and antimicrobial drugs; provides that rapidly alleviating the symptoms, healing of mucosal lesions and long-term reduction of peptic ulcer disease, reduced complications such as gastrointestinal bleeding, and reduced the need for prolonged secretion therapy.

Other effects related to acid inhibition:
In long-term treatment, the incidence of glandular cysts in the stomach may increase. These changes are a physiological consequence of pronounced inhibition of acid secretion. It is benign and appear to be reversible.

Decreased gastric acidity due to any means including proton pump inhibitors, increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with proton pump

inhibitors may slightly increase the risk of gastrointestinal infections such as Salmonella and Campylobacter, and possibly also in hospitalized patients, such as Clostridium difficile.

Serum gastrini increases in response to decreased acid secretion during treatment with secretory-blocking medicinal products. At the same time, chromogranin A (CgA) increases due to decreased gastric acidity. Increased CgA level may prevent the investigation of neuroendocrine tumors.In order to avoid this, omeprazole treatment should be stopped 5 days before CgA measurements.If CgA and gastrin levels do not return to normal after 5 days, measurements should be repeated 14 days after discontinuation of omeprazole therapy.

During long-term treatment with omeprazole, an increase in the number of Entero chromaffin-like (ECL) cells in some patients (in children and adults), probably associated with increased serum gastrin levels, was observed. It is thought that the findings do not have a clinical meaning.

5.2 Pharmacokinetic properties

General properties:

Distribution:

The apparent volume of distribution in healthy subjects is approximately 0.3 l/kg body weight. Omeprazole is bound to proteins at 97% rate.

Biotransformation:

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.

Elimination:

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 with no tendency for accumulation during once-daily administration. Approximately 80% of the intravenously administered dose is excreted as metabolites, and the rest is excreted by faeces mainly due to bile secretion.

The area under the curve (EAA) in the plasma-time measurement of omeprazole is increased by repeated applications, possibly due to a decrease in systemic cleavage caused by inhibition of CYP2C19 enzyme by omeprazole and / or its metabolites (eg, sulfone).
No metabolite has been found to have any effect on gastric acid secretion.

Characteristic features of patients

Impaired renal function:

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

Hepatic impairment:
AUC increases in patients with insufficient liver function, but oral administration of omeprazole once daily did not cause any accumulation.

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

Children:
The experience on use of omeprazole I.V. in children is limited.

Weak metabolizers:
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.

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 H -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 PROPERTIES
6.1 List of excipients
OMEPREFUL consists of one vial and one solvent bulb.

In each vial:
Sodium hydroxide

In each solvent ampoule:
Polyethylene glycol 400
Citric acid monohydrate
Water for injection

6.2 Incompatibilities
There is no known incompatibility when used as recommended.

6.3 Shelf life
Unopened package (carton box): 24 months at room temperature below 25 °C.
The vials removed from the outer packaging must be protected from light and can be stored for up to 24 hours in normal room light.
The prepared solution for injection can be stored at 25 °C for 4 hours.

6.4 Special precautions for storage
It has been shown to be chemically and physically stable for 12 hours at 2-8ºC in the

refrigerator, 4 hours at 25 °C after preparation.

6.5 Nature and contents of container

Vial: Type I colorless glass vial sealed with bromobutyl plug and transparent flip off cap in box
Solvent ampoule: Type I colorless glass ampoule

6.6 Special precautions for disposal and other handling

Unused products or waste materials must be disposed of in accordance with the "Medical Wastes Control Regulation" and the "Packaging and Packaging Wastes Control Regulations"

7. MARKETING AUTHORISATION HOLDER

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