1.	**Name of the Medical Product**
	1.1 Product Name : **NOPYLO KIT** (Combikit of Amoxicillin Capsules BP 500 mg & Clarithromycin Tablets BP 500mg & Omeprazole Gastro-resistant Capsules BP 20 mg)

1.2 Strength :

Each combikit contains:

1) Amoxicillin Capsules BP 500mg (4 Capsules)
Each hard gelatin capsules contains:
Amoxicillin Trihydrate BP
Equivalent to Amoxicillin 500mg
Approved colour used in hard gelatin capsule shell.

2) Clarithromycin Tablets BP 500 mg (2 Tablets)
Each film coated tablet contains:
Clarithromycin BP 500mg
Colour: Titanium Dioxide

3) Omeprazole Gastro-resistant Capsule BP 20 mg (2 Capsules)
Each hard gelatin capsule contains:
Omeprazole BP 20 mg
(As enteric coated pellets)
Approved colour used in hard gelatin capsule shell

	1.3 Pharmaceutical Dosage Form : Oral Solid (Tablets & Capsules in Combikit)
2.	**Qualitative & Quantitative Composition:** Each combikit contains: 1) Amoxicillin Capsules BP 500mg (4 Capsules) Each hard gelatin capsules contains: Amoxicillin Trihydrate BP Equivalent to Amoxicillin 500mg Approved colour used in hard gelatin capsule shell. 2) Clarithromycin Tablets BP 500 mg (2 Tablets) Each film coated tablet contains: Clarithromycin BP 500mg Colour: Titanium Dioxide 3) Omeprazole Gastro-resistant Capsule BP 20 mg (2 Capsules) Each hard gelatin capsule contains: Omeprazole BP 20 mg (As enteric coated pellets) Approved colour used in hard gelatin capsule shell For a full list of excipients, see section 6.1 of SmPC
3.	**Pharmaceutical Form:**
	Amoxicillin Capsules BP 500 mg : Size “0” hard gelatin Capsule of yellow body & maroon cap containing white granular powder.
	Clarithromycin Tablets BP 500 mg : White colored, capsule shaped, biconvex, film coated tablet, plain on one side and break line on other side. Omeprazole Gastro-resistant Capsule BP 20 mg : Hard gelatin capsule of Size □2□ having Pink Cap & Clear Transparent body containing white to off white coloured spherical pellets.
4.	**Clinical Particulars**

4.1 Therapeutic Indications:

- To reduce the development of drug-resistant bacteria and maintain the effectiveness of Nopylo Combikit and other antibacterial drugs, Nopylo Combikit should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.
- Eradication of Helicobacter pylori in Patients with Active Duodenal Ulcer or History of Duodenal Ulcer Disease - amoxicillin capsules, clarithromycin tablets and Omeprazole Gastro-resistant Capsules taken together are indicated for the treatment of patients with Helicobacter pylori infection and duodenal ulcer disease (active or one-year history) to eradicate H. pylori in adults. Eradication of H. pylori has been shown to reduce the risk of duodenal ulcer recurrence.

In patients who fail therapy with Nopylo combikit, perform susceptibility testing. If resistance to clarithromycin is demonstrated or susceptibility testing is not possible, institute alternative antimicrobial therapy.

4.2 Posology and Method of administration:

The recommended adult oral regimen is amoxicillin capsules 500 mg (2 capsules), clarithromycin tablets 500 mg and Omeprazole Gastro-resistant Capsules 20 mg each given twice daily, for 10 days, in the morning and evening before eating a meal. Inform patien ts that amoxicillin, clarithromycin and omeprazole should not be crushed or chewed, and should be swallowed whole.

In patients with an ulcer present at the time of initiation of therapy, an additional 18 days of omeprazole 20 mg once daily is recommended for ulcer healing and symptom relief.

4.3 Contraindications:

Combikit of Amoxicillin Capsules, Clarithromycin Tablets & Omeprazole Gastro-resistant Capsules is contraindicated in patients with a history of hypersensitivity to omeprazole, any macrolide antibiotic, or any penicillin. Hypersensitivity reactions to omeprazole may include anaphylaxis, anaphylactic shock, angioedema, bronchospasm, interstitial nephritis, and urticaria.

Hypersensitivity reactions to clarithromycin may include anaphylaxis, Stevens-Johnson syndrome, and toxic epidermal necrolysis.

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients on penicillin therapy. Although anaphylaxis is more frequent following parenteral therapy, it has occurred in patients on oral penicillins. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity and/or a history of sensitivity to multiple allergens. Before initiating therapy with amoxicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins or other allergens. Hypersensitivity reactions to amoxicillin may include

serum sickness like reactions, erythematous maculopapular rashes, erythema multiforme, Stevens-Johnson syndrome, exfoliative dermatitis, toxic epidermal necrolysis, acute generalized exanthematous pustulosis, hypersensitivity vasculitis and urticaria.

4.4 Special warning and precautions for use:
Fetal Risk and Clarithromycin

Clarithromycin has demonstrated adverse effects on pregnancy outcomes and/or embryofetal development in monkeys, rats, mice, and rabbits at doses that produced plasma concentrations 2 to 17 times the serum concentrations achieved in humans at the maximum recommended human dose. Clarithromycin should be used in pregnant women only in clinical circumstances where no alternative therapy is appropriate, and the potential benefit to the patient outweighs the potential risk to the fetus.

Colchicine Toxicity with Clarithromycin

There have been postmarketing reports of colchicine toxicity, some fatal, with concomitant use of clarithromycin and colchicine, especially in the elderly, some of which occurred in patients with renal insufficiency. Monitor patients for clinical symptoms of colchicine toxicity.

Myasthenia Gravis

Exacerbation of symptoms of myasthenia gravis and new onset of symptoms of myasthenic syndrome have been reported in patients receiving clarithromycin therapy. Monitor patients for symptoms.

Clostridium difficile-associated diarrhea

Clostridium difficile-associated diarrhea (CDAD) has been reported with use of clarithromycin and amoxicillin, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of C. difficile. C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin-producing strains of C. difficile cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents. If CDAD is suspected or confirmed, ongoing antibiotic use not directed against C. difficile may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of C. difficile, and surgical evaluation should be instituted as clinically indicated.

Concomitant Gastric Malignancy

Symptomatic response to therapy with omeprazole does not preclude the presence of gastric malignancy.

Acute Interstitial Nephritis

	Acute interstitial nephritis (AIN) has been observed in patients taking PPIs including omeprazole. Acute interstitial nephritis may occur at any point during PPI therapy and is

generally attributed to an idiopathic hypersensitivity reaction. Discontinue omeprazole if AIN develops.

Development of Bacterial Superinfections

The possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy with combikit of Amoxicillin Capsules, Clarithromycin Tablets & Omeprazole Gastro-resistant Capsules due to the clarithromycin and amoxicillin components. If superinfections occur, it should be discontinued and appropriate therapy instituted.

Mononucleosis and Ampicillin

A high percentage of patients with mononucleosis who receive ampicillin develop an erythematosus skin rash. Thus, administration of ampicillin-class antibiotics is not recommended in patients with mononucleosis.

Development of Drug Resistant Bacteria

Prescribing clarithromycin or amoxicillin in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug resistant bacteria.

4.5 Interactions with other medicinal products and other forms of Interactions :

Effect of Omeprazole

- Omeprazole is a substrate and an inhibitor of CYP2C19 in vivo, a substrate of CYP3A4 in vivo, and an inhibitor of CYP2C19 in vitro. Therefore, omeprazole may affect the metabolism and plasma concentrations of drugs that are metabolized by these CYP enzymes. Although in healthy subjects no interaction with theophylline or propranolol was reported, there have been reports of an interaction with other drugs metabolized via the CYP enzyme system (e.g., cyclosporine, disulfiram, benzodiazepines). Carefully monit or patients taking these drugs to determine if dosage adjustments of these drugs are necessary when taken concomitantly with omeprazole.

Effect of Clarithromycin

- Clarithromycin is a substrate and inhibitor of CYP3A enzymes. Coadministration of clarithromy cin with drugs metabolized by CYP3A may be associated with elevations in drug concentrations that could increase the therapeutic and adverse effects of the concomitant drug. There have been reports of CYP3A -based interactions of erythromycin and/or clarith romycin with cyclosporine, tacrolimus, alfentanil, rifabutin, methylprednisolone, cilostazol, and bromocriptine. In addition, there have been reports of interactions of erythromycin or clarithromycin with drugs not thought to be metabolized by CYP3A, inclu ding: hexobarbital, phenytoin, and valproate.

P-glycoprotein (Pgp). The clarithromycin component of combikit of Amoxicillin Capsules, Clarithromycin Tablets & Omeprazole Gastro-resistant Capsules is known to inhibit CYP3A and Pgp. When clarithromycin and colchicine are administered together, inhibition of Pgp and/or CYP3A by clarithromycin may lead to increased plasma exposure to colchicine. Monitor patients for clinical symptoms of colchicine toxicity.

- Ergotamine/Dihydroergotamine

Ergotamine/dihydroergotamine plasma concentrations may increase when administered concomitantly with combikit of Amoxicillin Capsules, Clarithromycin Tablets & Omeprazole Gastro-resistant Capsules.

- Pimozide

The coadministration of pimozide and combikit of Amoxicillin Capsules, Clarithromycin Tablets & Omeprazole Gastro-resistant Capsules may increase the pimozide plasma concentrations due to an interaction with the clarithromycin component of combikit of Amoxicillin Capsules, Clarithromycin Tablets & Omeprazole Gastro-resistant Capsules.

- Antiarrhythmics

Concurrent use of antiarrhythmic drugs and combikit of Amoxicillin Capsules, Clarithromycin Tablets & Omeprazole Gastro-resistant Capsules may potentiate the antiarrhythmic effects due to an interaction with the clarithromycin component of Combikit.

- Anticoagulants

The simultaneous administration of anticoagulants and combikit of Amoxicillin Capsules, Clarithromycin Tablets & Omeprazole Gastro-resistant Capsules may alter the anticoagulant effects of warfarin and other oral anticoagulants due to an interaction with the omeprazole and clarithromycin components of Combikit.

- Antiretroviral Drugs

Concurrent use of antiretroviral agents and combikit of Amoxicillin Capsules, Clarithromycin Tablets & Omeprazole Gastro-resistant Capsules may alter the antiretroviral effects due to interactions with the omeprazole or clarithromycin components of Combikit. Omeprazole has been reported to interact with some antiretroviral drugs such as atazanavir, nelfinavir and saquinavir. Concomitant use of atazanavir or nelfinavir with omeprazole is not recommended unless the benefits of taking atazanavir or nelfinavir with combikit of Amoxicillin Capsules, Clarithromycin Tablets & Omeprazole Gastro-resistant Capsules outweigh the risks.

	Coadministration of atazanavir or nelfinavir with proton pump inhibitors is expected to substantially decrease atazanavir or nelfinavir plasma concentrations and thereby reduce the therapeutic effect of either of these drugs.

Coadministration of saquinavir with omeprazole may increase the serum concentrations of saquinavir. Dose reduction of saquinavir should be considered when coadministered with Combikit.

- Cilostazol

Concomitant administration of combikit of Amoxicillin Capsules, Clarithromycin Tablets & Omeprazole Gastro-resistant Capsules and cilostazol may increase systemic exposure of cilostazol due to an interaction with the omeprazole component of Nopylo. Therefore, a dose reduction of cilostazol by 50% should be considered when concomitantly administered with Combikit.

- Tacrolimus

Concomitant administration of combikit of Amoxicillin Capsules, Clarithromycin Tablets & Omeprazole Gastro-resistant Capsules and tacrolimus may increase the serum concentrations of tacrolimus due to an interaction with the omeprazole component of Combikit. Frequent monitoring of whole blood trough concentrations of tacrolimus is recommended when concomitantly administered with Combikit.

- Theophylline

Combikit of Amoxicillin Capsules, Clarithromycin Tablets & Omeprazole Gastroresistant Capsules use in patients who are receiving theophylline may be associated with an increase of serum theophylline concentrations due to an interaction with the clarithromycin component of Combikit. Monitoring of serum theophylline concentrations should be considered for patients receiving high doses of theophylline or with baseline concentrations in the upper therapeutic range.

- Carbamazepine

The simultaneous administration of carbamazepine and combikit of Amoxicillin Capsules, Clarithromycin Tablets & Omeprazole Gastro-resistant Capsules may alter the effect of carbamazepine due to an interaction with the clarithromycin component of combikit. Concomitant administration of single doses of clarithromycin and carbamazepine has been shown to result in increased plasma concentrations of carbamazepine. Blood level monitoring of carbamazepine should be considered when administered concomitantly with Combikit.

- Sildenafil

The systemic exposure of sildenafil may increase when it is administered concomitantly with combikit of Amoxicillin Capsules, Clarithromycin Tablets & Omeprazole Gastro-resistant Capsules due to an interaction with the clarithromycin component of Combikit ; consider a reduction in sildenafil dosage.

	• HMG-CoA Reductase Inhibitors (Statins) Concurrent use of HMG-CoA reductase inhibitors (statins) and combikit of Amoxicillin Capsules, Clarithromycin Tablets & Omeprazole Gastro-resistant Capsules may alter the effect of HMG-CoA due to an interaction with the clarithromycin component of Combikit. As with other macrolides, clarithromycin

has been reported to increase concentrations of statins (e.g., lovastatin and simvastatin). Rare reports of rhabdomyolysis have been reported in patients taking these drugs concomitantly.

- Triazolobenziodidiazepines (e.g., triazolam and alprazolam) and related Benzodiazepines (e.g., midazolam)

The effect of triazolobenziodidiazepines/related benzodiazepines may be altered when administered concomitantly with combikit of Amoxicillin Capsules, Clarithromycin Tablets & Omeprazole Gastro-resistant Capsules due to an interaction with the clarithromycin component.

- Probenecid

Probenecid decreases the renal tubular secretion of amoxicillin. Concurrent use of combikit of Amoxicillin Capsules, Clarithromycin Tablets & Omeprazole Gastroresistant Capsules and probenecid may result in increased and prolonged blood concentrations of the amoxicillin component of Combikit.

- Drugs for which Gastric pH can affect Bioavailability

Due to its effects on gastric acid secretion, omeprazole can reduce the absorption of drugs where gastric pH is an important determinant of their bioavailability. As with other drugs that decrease the intragastric acidity, the absorption of drugs such as ketoconazole, atazanavir, iron salts, erlotinib, and mycophenolate mofetil can decrease, while the absorption of drugs such as digoxin can increase during treatment with omeprazole. Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10% (30% in two subjects). Coadministration of digoxin with omeprazole is expected to increase the systemic exposure of digoxin. Therefore, patients may need to be monitored when digoxin is taken concomitantly with omeprazole.

Coadministration of omeprazole in healthy subjects and in transplant patients receiving mycophenolate mofetil has been reported to reduce the exposure to mycophenolic acid (MPA), the active moiety, possibly due to a decrease in MPA solubility at an increased gastric pH. The clinical relevance of reduced MPA exposure on organ rejection has not been established in transplant patients receiving proton pump inhibitors (PPIs) and mycophenolate mofetil. Use omeprazole with caution in transplant patients receiving mycophenolate mofetil.

- Drug-Laboratory Test Interactions

High urine concentrations of ampicillin may result in false-positive reactions when testing for the presence of glucose in urine using Benedict's Solution or Fehling's Solution. Since this effect may also occur with amoxicillin, it is recommended that glucose tests based on enzymatic glucose oxidase reactions be used. Following

	administration of ampicillin to pregnant women, a transient decrease in plasma concentration of total conjugated estradiol, estriol-glucuronide, conjugated estrone, and estradiol has been noted. This effect may also occur with amoxicillin.

	4.6 Pregnancy and Lactation: Pregnancy

	Pregnancy Category C (based on animal studies of omeprazole and clarithromycin) There are no adequate and well controlled studies of omeprazole, clarithromycin, or amoxicillin (used separately or together) in pregnant women. Clarithromycin demonstrated adverse developmental effects in four animal species at clinically relevant doses. Omeprazole increased embryo-fetal loss in rabbits, but animal studies and multiple human studies do not show an increased risk for major malformations. Nopylo kit should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus and there is no appropriate alternative therapy. Labor and Delivery Omeprazole: Several studies have reported no apparent adverse short-term effects on the infant when single dose oral or intravenous omeprazole was administered to over 200 pregnant women as premedication for cesarean section under general anesthesia. Amoxicillin: Oral ampicillin-class antibiotics are poorly absorbed during labor. Studies in guinea pigs showed that intravenous administration of ampicillin slightly decreased the uterine tone and frequency of contractions, but moderately increased the height and duration of contractions. However, it is not known whether amoxicillin affects labor or delivery in humans. Nursing Mothers Nopylo kit contains omeprazole, clarithromycin, and amoxicillin. Information on use of each product during lactation is provided below. Omeprazole: Breast milk concentrations of omeprazole were measured in the breast milk of one woman following oral administration of 20 mg. The peak concentration was 20 mcg/L, less than 7% of the peak maternal serum concentration. Based on this information, the estimated infant daily dose in an exclusively human-milk fed infant is 3 mcg/kg/day. However, due to the potential for tumorigenicity shown for omeprazole in rat carcinogenicity studies, a decision should be made whether to discontinue nursing or express and discard milk during Nopylo Kit treatment. Clarithromycin: It is not known whether clarithromycin is excreted in human milk. However, other macrolide antibiotics are excreted in human milk. Clarithromycin is found in animal milk. Caution should be exercised when clarithromycin is administered to a nursing woman. Amoxicillin: Penicillins are excreted in human milk. Amoxicillin use by nursing mothers may lead to sensitization of infants. Caution should be exercised when amoxicillin is administered to a nursing woman. Pediatric Use The safety and effectiveness of combikit of Amoxicillin Capsules, Clarithromycin Tablets & Omeprazole Gastro-resistant Capsules for pediatric patients with H. pylori have not been established. Geriatric Use Omeprazole: In a published study, Omeprazole was administered to over 2000 elderly individuals (≥ 65 years of age) in clinical trials in the U.S. and Europe. There were no differences in safety and effectiveness between the elderly and younger subjects. Other reported clinical experience has not identified differences in response between the elderly and younger subjects, but greater sensitivity of some older individuals cannot be ruled out. Pharmacokinetic studies have shown the elimination rate was somewhat decreased in the elderly and bioavailability was increased. The plasma clearance of omeprazole was 250 mL/min (about half that of young volunteers) and its plasma half-life averaged one hour, about twice that of young healthy volunteers. However, no dosage adjustment is necessary in the elderly.

	Clarithromycin: In a published steady-state study in which healthy elderly subjects (age 65 to 81 years old) were given 500 mg every 12 hours, the maximum serum concentrations and area under the curves of clarithromycin and 14-OH clarithromycin were increased compared to those achieved in healthy young adults. These changes in pharmacokinetics

parallel known age-related decreases in renal function. In clinical trials, elderly patients did not have an increased incidence of adverse events when compared to younger patients. Amoxicillin: In a published study, an analysis of clinical studies of amoxicillin was conducted which determined whether subjects aged 65 and over respond differently from younger subjects. Of the 1811 subjects treated with amoxicillin, 85% were < 60 years old, 15% were ≥ 61 years old and 7% were ≥ 71 years old. This analysis and other reported clinical experience have not identified differences in responses between the elderly and younger patients, but a greater sensitivity of some older individuals cannot be ruled out. This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Renal Impairment:

In the presence of severe renal impairment with or without coexisting hepatic impairment, prolonged dosing intervals for the clarithromycin component may be appropriate.

Hepatic Impairment:

It is recommended to avoid the use of Nopylo Kit in patients with hepatic impairment.

4.7 Effects on ability to drive and use machine:

There is no information available for Omeprazole, clarithromycin and amoxicillin for its effects on ability to drive and use machines.

4.8 Undesirable Effects:
The following serious adverse reactions are described for Combikit consisting of Omeprazole capsules, clarithromycin tablets and amoxicillin capsules:

- Hypersensitivity
- Myasthenia Gravis
- *Clostridium difficile*-associated diarrhea

Clinical Trials Experience
In published clinical trials using triple therapy with omeprazole, clarithromycin, and amoxicillin, no adverse reactions unique to triple therapy were observed. Adverse reactions observed were limited to those previously reported with omeprazole, clarithromycin, or amoxicillin alone. The most frequent adverse reactions observed in clinical trials using combination therapy with omeprazole, clarithromycin, and amoxicillin (n = 274) were diarrhea (14%), taste perversion (10%), and headache (7%). None of these occurred at a higher frequency than that reported by patients taking antimicrobial agents alone.

Adverse Reactions for the Individual Components of combikit of Amoxicillin Capsules, Clarithromycin Tablets & Omeprazole Gastro-resistant Capsules:

The safety data below reflect exposure to omeprazole delayed-release capsules and clarithromycin worldwide in clinical trials for various indications using doses and durations of therapy that may differ from how they are used as a component of combikit.

Omeprazole:

Additional adverse reactions that were reported with an incidence rate ≥ 1% included acid regurgitation (1.9%), upper respiratory infection (1.9%), constipation (1.5%), dizziness (1.5%), rash (1.5%), asthenia (1.3%), back pain (1.1%), and cough (1.1%).
The clinical trial safety profile in patients greater than 65 years of age was similar to that in patients 65 years of age or less.

Clarithromycin:
The most frequently reported events in adults were diarrhea (3%), nausea (3%), abnormal taste (3%), dyspepsia (2%), abdominal pain/discomfort (2%), and headache (2%). Most of these events were described as mild or moderate in severity. Of the reported adverse events, only 1% were described as severe. Fewer than 3% of adult patients without mycobacterial infections discontinued therapy because of drug-related side effects.

Amoxicillin:
Gastrointestinal: Nausea, vomiting, diarrhea, and hemorrhagic/Clostridium difficileassociated colitis. Onset of Clostridium difficile-associated diarrhea may occur during or after antibiotic treatment.

Hypersensitivity Reactions: Serum sickness like reactions, erythematous maculopapular rashes, erythema multiforme, Stevens-Johnson syndrome, exfoliative dermatitis, toxic epidermal necrolysis, acute generalized exanthematous pustulosis, hypersensitivity vasculitis and urticaria have been reported.

Reactions are more likely to occur in individuals who have previously demonstrated hypersensitivity to penicillins and in those with a history of allergy, asthma, hay fever, or urticaria.

Hepatic: A moderate rise in AST (SGOT) and/or ALT (SGPT) has been noted, but the significance of this finding is unknown. Hepatic dysfunction including cholestatic jaundice, hepatic cholestasis and acute cytolytic hepatitis have been reported.

Renal: Crystalluria has also been reported.

Hemic and Lymphatic Systems: Anemia, including hemolytic anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia and agranulocytosis have been reported during therapy with penicillins.

These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena.

	Nervous System/Psychiatric: Reversible hyperactivity, agitation, anxiety, insomnia, confusion, behavioral changes, and/or dizziness have been reported rarely. Miscellaneous: Tooth discoloration (brown, yellow, or gray staining) has been rarely reported. Most reports occurred in pediatric patients. Discoloration was reduced or eliminated with brushing or dental cleaning in most cases.

	Changes in Laboratory Values: Changes in laboratory values with possible clinical significance were as follows: Hepatic – elevated SGPT (ALT) less than 1%, SGOT (AST) less than 1%, GGT less than 1%, alkaline phosphatase less than 1%, LDH less than 1%, total bilirubin less than 1%; Hematologic – decreased WBC less than 1%, elevated prothrombin time 1%; Renal – elevated BUN 4%, elevated serum creatinine less than 1%. GGT, alkaline phosphatase, and prothrombin time data are from adult studies only.
	4.9 Overdosage: There is neither a pharmacologic basis nor data suggesting an increased toxicity of the combination compared to individual components. **Omeprazole**: Doses of Omeprazole ranged up to 2400 mg (120 times the usual recommended clinical dose). Manifestations were variable, but included confusion, drowsiness, blurred vision, tachycardia, nausea, vomiting, diaphoresis, flushing, headache, dry mouth, and other adverse reactions similar to those seen in normal clinical experience. Symptoms were transient, and no serious clinical outcome has been reported when omeprazole was taken alone. No specific antidote for omeprazole overdosage is known. Omeprazole is extensively protein bound and is, therefore, not readily dialyzable. In the event of overdosage, treatment should be symptomatic and supportive. Single oral doses of omeprazole at 1350, 1339, and 1200 mg/kg were lethal to mice, rats, and dogs, respectively. Animals given these doses showed sedation, ptosis, tremors, convulsions, and decreased activity, body temperature, and respiratory rate and increased depth of respiration. **Clarithromycin**: Overdosage of clarithromycin can cause gastrointestinal symptoms such as abdominal pain, vomiting, nausea, and diarrhea. Adverse reactions accompanying overdosage should be treated by the prompt elimination of unabsorbed drug and supportive measures. As with other macrolides, clarithromycin serum concentrations are not expected to be appreciably affected by hemodialysis or peritoneal dialysis. **Amoxicillin:** In case of overdosage, discontinue medication, treat symptomatically, and institute supportive measures as required. If the overdosage is very recent and there is no contraindication, an attempt at emesis or other means of removal of drug from the stomach may be performed. Crystalluria, in some cases leading to renal failure, has also been reported after amoxicillin overdosage in adult and pediatric patients. In case of overdosage, adequate fluid intake and diuresis should be maintained to reduce the risk of amoxicillin crystalluria. Renal impairment appears to be reversible with cessation of drug administration. High blood concentrations may occur more readily in patients with impaired renal function because of decreased renal clearance of amoxicillin. Amoxicillin can be removed from circulation by hemodialysis. In case of an overdose, patients should contact a physician, poison control center, or emergency room.

5.	**Pharmacological properties**
	Pharmacotherapeutic group: Amoxicillin : beta-lactam family of antibiotics ATC Code: J01CA04 Clarithromycin : macrolide antibiotics ATC Code: J01FA09 Omeprazole : Proton pump inhibitors

ATC Code: A02BC01

5.1 Pharmacodynamic Properties:

Mechanism of Action:

Omeprazole, an antisecretory drug with the substituted benzimidazoles , suppresses gastric acid secretion by specific inhibition of the H+ /K+ ATPase enzyme system at the secretory surface of the gastric parietal cell. Because this enzyme system is regarded as the acid (proton) pump within the gastric mucosa, omeprazole has been characterized as a gastric acid-pump inhibitor, in that it blocks the final step of acid production. This effect is dose - dependent and leads to inhibition of both basal and stimulated acid secretion irrespective of the stimulus. Omeprazole can also ex hibit anti-bacterial activity depending on the culture conditions. Animal studies indicate that after rapid disappearance from plasma, omeprazole can be found within the gastric mucosa for a day or more.

Clarithromycin exerts its antibacterial activity by binding to the 50S ribosomal subunit of susceptible microorganisms resulting in inhibition of protein synthesis. Amoxicillin acts through the inhibition of biosynthesis of cell wall mucopeptide.

Activity in vitro and in vivo : Triple therapy with omeprazo le, clarithromycin and amoxicillin has been shown to be active against most strains of Helicobacter pylori in vitro and in clinical infections as indicated. In vitro studies show that chloramphenicol, macrolides, sulfonamides, and tetracyclines may interf ere with bactericidal effects of penicillin; however, the clinical significance of this interaction is not well documented.

Drug Resistance:

Helicobacter pylori Pretreatment Resistance

In the study conducted with Innovator product,Clarithromycin pretreatment resistance rates were 9.3% (41/439) in omeprazole/clarithromycin/amoxicillin triple therapy studies.

Amoxicillin pretreatment susceptible isolates (≤ 0.25 µg/mL) were found in 99.3% (436/439) of the patients in the omeprazole/c larithromycin/amoxicillin triple therapy studies.

Amoxicillin pretreatment minimum inhibitory concentrations (MICs) > 0.25 µg/mL occurred in 0.7% (3/439) of the patients, all of whom were in the clarithromycin and amoxicillin study arm. One patient had an unconfirmed pretreatment amoxicillin minimum inhibitory concentration (MIC) of > 256 µg/mL by Etest.

5.2 Pharmacokinetics Properties:

Omeprazole delayed-release Capsules:

Absorption and Distribution

Omeprazole delayed-release Capsules contain an enteric coated pellets formulation of omeprazole (because omeprazole is acid-labile), so that absorption of omeprazole begins only after the granules leave the stomach. Absorption is rapid, with peak plasma concentrations of omeprazole occurring within 0.5 to 3.5 hours. Peak plasma concentrations of omeprazole and AUC are approximately proportional to doses up to 40 mg, but because of a saturable first-pass effect, a greater than linear response in peak plasma concentration and AUC occurs with doses greater than 40 mg. Absolute bioavailability (compared with intravenous administration) is about 30-40% at doses of 20-40 mg, due in large part to presystemic metabolism. In healthy subjects the plasma half-life is 0.5 to 1 hour, and the total body clearance is 500-600 mL/min. The bioavailability of omeprazole increases slightly upon repeated administration of Omeprazole Delayed-Release Capsules.

Metabolism and Excretion

	Omeprazole is extensively metabolized by the cytochrome P450 (CYP) enzyme system. Following single dose oral administration of a buffered solution of omeprazole, little if any unchanged drug was excreted in urine. The majority of the dose (about 77%) was eliminated in urine as at least six metabolites. Two were identified as hydroxyomeprazole and the corresponding carboxylic acid. The remainder of the dose was recoverable in feces. This implies a significant biliary excretion of the metabolites of omeprazole. Three metabolites have been identified in plasma – the sulfide and sulfone derivatives of omeprazole, and hydroxyomeprazole. These metabolites have very little or no antisecretory activity. Clarithromycin Tablets: Clarithromycin is rapidly absorbed from the gastrointestinal tract after oral administration. The absolute bioavailability of 250 mg clarithromycin tablets was approximately 50%. For a single 500 mg dose of clarithromycin, food slightly delays the onset of clarithromycin absorption, increasing the peak time from approximately 2 to 2.5 hours. Food also increases the clarithromycin peak plasma concentration by about 24%, but does not affect the extent of clarithromycin bioavailability. Food does not affect the onset of formation of the antimicrobially active metabolite, 14-OH clarithromycin or its peak plasma concentration but does slightly increase the extent of metabolite formation, indicated by an 11% decrease in area under the plasma concentration-time curve (AUC). Therefore, clarithromycin tablets may be given without regard to food. In nonfasting healthy human subjects (males and females), peak plasma concentrations were attained within 2 to 3 hours after oral dosing. Steady-state peak plasma clarithromycin concentrations were attained within 3 days and were approximately 3 to 4 µg/mL with a 500 mg dose administered every 8 to 12 hours. The elimination half-life of clarithromycin was 5 to 7 hours with 500 mg administered every 8 to 12 hours. The nonlinearity of clarithromycin pharmacokinetics is slight at the recommended dose of 500 mg administered every 8 to 12 hours. With a 500 mg every 8 to 12 hours dosing, the peak steady-state concentration of 14-OH clarithromycin is up to 1 µg/mL, and its elimination half-life is about 7 to 9 hours. The steady-state concentration of this metabolite is generally attained within 3 to 4 days. After a 500 mg tablet every 12 hours, the urinary excretion of clarithromycin is approximately 30%. The renal clearance of clarithromycin approximates the normal glomerular filtration rate. The major metabolite found in urine is 14-OH clarithromycin, which accounts for an additional 10% to 15% of the dose with a 500 mg tablet administered every 12 hours. The steady-state concentrations of clarithromycin in subjects with impaired hepatic function did not differ from those in normal subjects; however, the 14-OH clarithromycin concentrations were lower in the hepatically impaired subjects. The decreased formation of 14-OH clarithromycin was at least partially offset by an increase in renal clearance of clarithromycin in the subjects with impaired hepatic function when compared to healthy subjects. The pharmacokinetics of clarithromycin was altered in subjects with impaired renal function. In the presence of severe renal impairment with or without coexisting hepatic impairment, prolonged dosing intervals for clarithromycin may be appropriate.

	Amoxicillin Capsules: Amoxicillin is stable in the presence of gastric acid and may be given without regard to meals. It is rapidly absorbed after oral administration. It diffuses readily into most body tissues and fluids, with the exception of brain and spinal fluid, except when meninges are

	inflamed. The half-life of amoxicillin is 61.3 minutes. Most of the amoxicillin is excreted unchanged in the urine; its excretion can be delayed by concurrent administration of probenecid. In blood serum, amoxicillin is approximately 20% protein-bound. Orally administered doses of 500 mg amoxicillin capsules result in average peak blood concentrations 1 to 2 hours after administration in the range of 5.5 µg /mL to 7.5 µg /mL. Detectable serum concentrations are observed up to 8 hours after an orally administered dose of amoxicillin. Approximately 60% of an orally administered dose of amoxicillin is excreted in the urine within 6 to 8 hours.

	5.3 Preclinical Safety data: **Carcinogenesis, Mutagenesis, Impairment of Fertility** Omeprazole: In two 24-month carcinogenicity studies in rats, omeprazole at daily doses of 1.7, 3.4, 13.8, 44.0 and 140.8 mg/kg/day (about 0.7 to 57 times a human dose of 20 mg/day, as expressed on a body surface area basis) produced gastric ECL cell carcinoids in a dose-related manner in both males and females; the incidence of this effect was markedly higher in female rats, which had higher blood concentrations of omeprazole. Gastric carcinoids seldom occur in the untreated rat. In addition, ECL cell hyperplasia was present in all treated groups of both sexes. In one of these studies, female rats were treated with 13.8 mg omeprazole/kg/day (about 6 times a human dose of 20 mg/day, based on body surface area) for one year, and then followed for an additional year without the drug. No carcinoids were seen in these rats. An increased incidence of treatment-related ECL cell hyperplasia was observed at the end of one year (94% treated vs. 10% controls). By the second year the difference between treated and control rats was much smaller (46% vs. 26%) but still showed more hyperplasia in the treated group. Gastric adenocarcinoma was seen in one rat (2%). No similar tumor was seen in male or female rats treated for two years. For this strain of rat no similar tumor has been noted historically, but a finding involving only one tumor is difficult to interpret. In a 52-week toxicity study in Sprague-Dawley rats, brain astrocytomas were found in a small number of males that received omeprazole at dose levels of 0.4, 2, and 16 mg/kg/day (about 0.2 to 6.5 times the human dose on a body surface area basis). No astrocytomas were observed in female rats in this study or in males or females from a 2-year carcinogenicity study in Sprague-Dawley rats at the high dose of 140.8 mg/kg/day (about 57 times the human dose on a body surface area basis). A 78-week mouse carcinogenicity study of omeprazole did not show increased tumor occurrence, but the study was not conclusive. A 26-week p53 (+/–) transgenic mouse carcinogenicity study was not positive. Omeprazole was positive for clastogenic effects in an in vitro human lymphocyte chromosomal aberration assay, in one of two in vivo mouse micronucleus tests, and in an in vivo bone marrow cell chromosomal aberration assay. Omeprazole was negative in the in vitro Ames test, an in vitro mouse lymphoma cell forward mutation assay, and an in vivo rat liver DNA damage assay. Omeprazole at oral doses up to 138 mg/kg/day in rats (about 56 times the human dose on a body surface area basis) was found to have no effect on fertility and reproductive performance.
6.	**Pharmaceutical particulars**
	6.1 List of Excipients: **Amoxicillin capsules:** Magnesium Stearate, Size "0" hard gelatin Capsule Shells of yellow body & maroon cap

	Clarithromycin Tablets: Microcrystalline Cellulose, Lactose, Croscarmellose Sodium, Povidone, Purified Talc, Colloidal Anhydrous Silica, Magnesium Stearate, Hypromellose, Titanium dioxide, Propylene Glycol, Macrogol 6000, Isopropyl Alcohol, Purified Water. **Omeprazole Gastro-resistant Capsule:** Purified Talc, Size 2 Empty Hard Gelatin Capsule Shell, Pink Cap & clear transparent body.
	6.2 Incompatibilities: Not applicable
	6.3 Shelf life: 24 months
	6.4 Special Precautions for storage: Store below 30°C. Protect from light and moisture.
	6.5 Nature and contents of container: Nopylo Kit is supplied in a carton containing ten individual daily administration combikit with Patient Information leaflet. **Pack size**: 10 Combikits
	6.6 Special precautions for disposal: Not applicable
7.	**Marketing Authorization Holder:** Ajanta Pharma Limited Ajanta House, Charkop, Kandivli (West), Mumbai- 400 067, India Telephone : (0091) - 022- 66061000 Fax : (0091) - 022-66061200/300 e-mail : info@ajantapharma.com Manufactured by: UNI MEDICOLABS Plot No, 21-22, Pharmacity, Selaqui, Distt. Dehradun, Uttarakhand. India.
8.	**Marketing Authorization Numbers:** Not applicable
9.	**Date of first registration /renewal of the registration:** Not Applicable
10.	**Date of revision of text:** Feb 09, 2021