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Review Article

Yosprala, A new emerging gold standard drug for prevention of secondary cardiovascular and cerebrovascular events-an overview

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ABSTRACT

In India, there are roughly 30 million patients who suffer from heart diseases and two lakh surgeries have been performed every year. YOSPRALA- A new emerging drug approved by USFDA in September 2016 to treat Ischemic stroke, prophylaxis and gastric ulcer prophylaxis. In Yosprala the ingredients active is Aspirin which acts as an antiplatelet agent and omeprazole which acts a proton pump inhibitor, manufactured by Aralez pharmaceuticals Inc. yosprala is a delayed release, multi layered film coated tablet which consists of immediate release omeprazole layer surrounded by delayed release enteric coated aspirin tablet for administering orally. It is specifically indicated to patients who require aspirin to prevent secondary cerebrovascular and cardiovascular events and for the patients who are at a great risk of developing gastric ulcers associated by aspirin. Synthesis of prostaglandin and platelet aggregation can be inhibited by Aspirin. [H+/K+]-ATPase system of enzyme is inhibited by omeprazole which is responsible for gastric acid secretion present at the gastric parietal cell of secretory surface. An extensive survey of literature reveals that there is no analytical method has been reported yet for simultaneous estimation of aspirin and omeprazole by any analytical techniques.

Keywords: Aspirin; Aralez pharmaceuticals; Anti-platelet agent; Cerebro vascular; cardiovascular events; Omeprazole; Proton Pump Inhibitor; Yosprala; USFDA.

INTRODUCTION

Yosprala has been designed to support gastro and cardio vascular protection for patients who are at high risk to the proprietary intell-coat system. It has been designed for immediate release of 40mg of omeprazole occurs followed by enteric coated delayed release of 81mg or 325mg of aspirin strength dose. Aspirin component of yosprala reduces the non-fatal stroke and combined risk of death who have a risk of ischemic stroke. (This information is collected from Yosprala prescribing information,2016). USFDA approved Yosprala as a cerebrovascular and cardiovascular drug on September 14th 2016.(This information is reviewed and collected from Center watch drugs 2016). According to United States Pharmacopeia/National Formulatory (USP/NF)the excipients used in Yosprala all are inactive, The excipients used in the Yosprala formulation include Cornstarch, Pre-gelatinized starch, Microcrystalline cellulose, Colloidal silicon dioxide, Triethylcitrate, Stearicacid, Titaniumdioxide, Polysorbate 80, Methacrylic acid co-polymermdispersion, Glyceryl Monostearate, Sodium phosphate dibasic anhydrous, Yellow ironoxide, Polyethyleneglycol, Triacetin, Hydroxypropylmethylcellulose, Polydextrose, Polyethylenglycol, Talc, Povidone, FD&C Blue #2 and Povidone. (This information is collected from yosprala prescribing information, 2016). The omeprazole component efficacy in yosprala has been evaluated in 2randomized, 6-month, Double-Blind, Multicenter,Phse-3 Trials Phase 3 trials in patients who are suffering from cardiovascular and cerebrovascular events and were talking 325mg of aspirin for 3months and were expected to continue 6months of treatment, and they are at risk of developing GIT ulcers associated with aspirin who are of 55years of age or with 18 to 54 years of age who are documented with history of developing duodenal and gastric ulcers in the period of 5years before enrollment of study. The patients who received yosprala 40mg immediate release of omeprazole followed by 325 or 81mg enteric coated delayed release aspirin The formation of Duodenal and gastric ulcer was assessed by gastro duodenal endoscopy at screening and after treatment of 1, 3, and 6 months. (Whellan DJ et al. 2014, Aralez pharmaceuticals 0266, Aralez pharmaceuticals 0267).

Pharmacological review

The approved yosprala is an acquisition of Zontivity,

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Aspirin is used as a Gold Standard Drug for the people who experience a significant problems of heart attack in U.S. is used for the prevention of secondary Cerebro and cardiovascular events (ThomT, et al 2006).By the recent guidelines The American college of cardiology and American heart association confirm that the randomized controlled trials which were performed entering coated aspirin for primary prevention. (Bhatt D, et al. 2008).

Works done on drugs (aspirin and omeprazole)

An extensive literature survey reveals that there is no analytical method yet reported for simultaneous estimation of aspirin and omeprazole in combination by any analytical techniques. (Sanjaypai PN et al., 2016, Tukaram Kalyankar et al., 2016, Avani P. Khristi et al., 2015, Jadhv Santosh et al., 2015, Foram Jaysukhlal Chodvadiya et al., 2015, PM Chatrabhiji et al., 2014.PatelB et al., 2014, G. Nagarajan P et al., 2013, Anita S. kulkarni et al., 2012, Kalakonda Sri Nataraj et-al., 2012, R. Vijayaraghavan et al., 2011, Suresh Kumar S, et al., Jan-Mar 2010, D. kumaraswamy et al., 2010. Kirti S Topagi, et al., 2010, Ghulam Murtaza et al., 2011).

Clinical Benefits of Yosprala

Yosprala is approved by FDA based on the 2randomised double blind controlled clinical trials results. It reduces the risk of cardio vascular events such as ischemic stroke, nonfatal myocardial infarction, unstable angina pectoris and death in many patients.

It controls and reduces the sudden death in patients who are suffering with chronic stable angina pectoris.

It is not given as initial dose during onset f acute events such as myocardial infarction and coronary artery syndrome. (Whellan D et al., 2014 Oct).

Prescription Information: (This information is collected from Pub Chem sources)

Yosprala is a combination of aspirin and omeprazole. The Aspirin component acts as anti-platelet agent and omeprazole acts as proton pump inhibitor. Yosprala tablet is labeled as under the title "YOSPRALA-ASPIRIN AND OMEPRAZOLE TABLET, FILM COATED"

US FDA approval status

USFDA has approved Yosprala as once daily dose the fixed dose combination of Aspirin and Omeprazole an antiplatelet agent and proton pump inhibitor in UNITED STATES. U.S has approved yosprala as cardiovascular and cerebrovascular preventive drug in October 1stweek 2016, (This information is collected from center watch 2016) the published research shows the patient with high risk of coronary artery disease takes as a daily treatment. It is designed in such a way as enteric coated delayed release tablet to support the both actions of cardio vascular and Castro protection. (Miner PB Jr et al., 2013)

Description (This information is collected from yosprala med guide)

The active ingredients of Yosprala are Aspirin and Omeprazole, Aspirin acts as an antiplatelet agent and Omeprazole acts as a Proton Pump Inhibitor, Yosprala is an oval ,blue-green, delayed release, multi-layer film coated tablet consists of an enteric coated delayed release aspirin core surrounded by omeprazole layer for immediate release which is administered orally. The yosprala each delayed release tablet consists of either 81mg of aspirin and 40mg of omeprazole which is printed as 81/40mg and other dose strength containing 325mg aspirin and 40mg omeprazole printed as 325/40mg.

Aspirin which acts as an antiplatelet agent in yosprala is a white needle like crystalline powdered odorless drug. Aspirin when comes in contact with moisture leads to hydrolyses which gives acetic and salicylic acids which resembles the odor of vinegar. It is slightly soluble in water and highly soluble in lipids. Platelet COX-1 is irreversibly inhibited by Aspirin.

Omeprazole which is acts as Inhibitor of proton pump in yosprala is white to white off crystalline powdered drug which decompose at 155^{0}C and melts. As omeprazole is a weak base which is slightly soluble in acetone and isopropanol, very slightly soluble in water and freely soluble in solvents such as methanol and ethanol. It is stable under alkaline conditions and gets degraded in acid media depending upon the function of pH.

Mechanism of action

The combination of Aspirin and omeprazole is Yosprala. Aspirin (acetyl salicylic acid) which is an antiplatelet agent, inhibits both the aggregation of platelets and synthesis of prostaglandin and omeprazole which is a proton pump inhibitor belongs to the class of anti-secretory agents which are substituted benzimidazoles omeprazole suppresses gastric acid secretion by specifically inhibiting the [H+/K+] ATPase system of enzyme which are present at the gastric parietal cells are present at the secretory surface. The system of enzyme is the inhibitor of acid pump in the mucosal layer of gastric. The final step of acid production is blocked by omeprazole. As it is effect of dose dependent this inhibits the stimulated and basal acid secretion by independent of stimulus. (This information is reviewed and collected from Center watch drugs 2016**).**

Diagrammatic representation of release of yosprala drug (This information is collected from yosprala hcp)

USES: Aspirin, an antiplatelet medicine, is used

- In people who have risk of strokes such as mini strokes, transient ischemic attacks and death previously yosprala helps to reduce it.

- People suffering from heart attack, chest pain due to angina pectoris condition and which lead to death the risk of this condition is reduced by yosprala.
- Yosprala reduces the heart attack and sudden death risk in patients suffering from a chronic stable angina pectoris.
- The Aspirin component of yosprala improves blood flow in patients who have undergone the surgeries such as percutaneous Tran's luminal coronary angioplasty and coronary artery bypass grafting.
- Omeprazole component of yosprala reduces the development of ulcers formed in gastric region in patients who are older than 55years or previously have a history of ulcers caused by aspirin (This information is collected from Yosprala prescribing information, 2016)

Supplied and handling (This information is collected from Pub Chem)

- The high density polyethylene bottles with desiccant packets are used to pack the yosprala tablets.
- They are delayed release film coated, oval, blue-green tablets.
- The labeling is respectively done by black ink under labeling as follows,

  Aspirin 81mg/Omeprazole 40mg

  Aspirin325mg/Omeprazole40mg

Storage (This information is collected from yosprala med guide)

- Yosprala is stored at room temperature between 20^0C to 25^0C.
- It must be stored in the original container which should be tightly closed to protect from moisture.
- A desiccant packet is present in yosprala container to keep medicine dry.
- Do not throw away the desiccant packet of the container.
- Place away from the reach of children.

Limitations of use (This information is collected from yosprala prescribing information, 2016)

- yosprala will not reduce the gastro intestinal bleeding caused by aspirin.
- It cannot be given individually or interchanged as single component of aspirin and omeprazole.
- It is not used as initial dose of aspirin therapy during the onset of acute myocardial infarction, acute coronary syndrome or before percutaneous coronary intervention, the appropriate therapy is immediate release of aspirin. So, in Yosprala aspirin is given as delayed release formulation.

Study design (Whellan DJ, et al. Aralez pharmaceuticals 0266, 0267)

In yosprala the efficacy of omeprazole was evaluated in 2 randomized multicenter, double month in phase 3 trials for patients who were taking aspirin 325mg for more than 3months or greater than 6months and who are associated at risk of gastric ulcers at 55years of age or having a previous history from 18 to 54years of duodenal ulcers within 5years of enrollment studies. The gastric duodenal ulcer was reduced in patients who received yosprala 325mg delayed release aspirin 40mg immediate release omeprazole at screening and after 1, 3, and 6months of treatment.

Dosage and administration

Dose recommended

- Daily take one tablet
- It is available in two strength dosage form 81mg and 325mg of aspirin
- The effective dose for prevention of secondary cardiovascular and cerebrovascular events is 81mg and has been generally accepted.
- The need for 325mg should be considered by providers and refer this to Current clinical practice guidelines.

Instructions for administration

- Yosprala should be taken as a daily dose 60minutes before meal, should be swallowed whole with liquid.
- The tablet should not be chewed, crushed or dissolved.
- Yosprala should be used in lowest effective dose based on the treatment of patient individually.
- The potential dose dependent should be avoided which may cause adverse reactions which includes bleeding.
- If a patient has missed a yosprala dose advice him/her to take it immediately as soon as possible if you remember at a time of next dose skip the missed dose.
- The sudden stop of taking yosprala may increase the risk of heart attack or stroke.
- Stopping of yosprala leads to death shortly.

Contraindications

Yosprala is contraindicated in:

- Yosprala is contraindicated to the patients having allergy to aspirin and other non-steroidal anti-

inflammatory drugs and who are having syndrome of nasal polyps, asthma and rhinitis.

- In pediatric patients who are suspected of viral infections with fever or without.
- The aspirin component of yosprala causes Angioedema. Asthma and severe Urticaria.
- The concomitant Aspirin usage leads to the risk of Reyes syndrome in illnesses of viral.
- It is also contraindicated in patients having hypersensitive reactions to aspirin, omeprazole and its derivatives in any of the excipients.
- It is also contra indicated in patients receiving proton pump inhibitor and rilpivirine containing products.

Adverse effects

- Stomach pain or discomfort caused by gastritis,
- Nausea,
- Diarrhea,
- Gastric polyps,
- Non-cardiac chest pain.

Drug interaction studies

Yosprala effect on other drugs

The omeprazole is a time dependent inhibitor of CYP2C19 when other drugs are administered which increase the systemic exposure which is CYP2C19 substrate; the omeprazole administration will alter the pH of gastric and systemic exposure for drugs which are having soluble dependent pH.

Antiretroviral: Rilpivirine, Atazanavir drugs decreases concentration of serum when given in combination of omeprazole.

Rilpivirine: The AUC has been decreased by 40%, C_{max} -40%, C_{min}-33% the multiple doses of rilpivirine-150mg and omeprazole-20mg daily.

Nelfinavir*:* The AUC has been decreased by 36% and 92%, C_{max} -37% and 89%, C_{min} -39% and 75% the multiple dose of Nelfinavir -1250mg and omeprazole-40mg twice daily.

Atazanavir: The AUC has been decreased by 94%, C_{max} -96%, C_{min}-95% and 75% the multiple dose of Atazanavir -400mg and omeprazole-40mg twice daily.

Saquinavir: The AUC has been increased by 82%, C_{max} -75%, C_{min}-106%, the multiple dose of saquinavir/Ritonavir (1000/100mg) twice daily for 15days with 40mg omeprazole. Therefore, the combination causes toxicity by clinical and laboratory monitoring.

Clopidogrel: 72 healthy subjects were given Clopidogrel (300 mg loading dose followed by 75 mg per day) alone and also in combination of omeprazole (80 mg at the same time as Clopidogrel) for 5days in a cross over clinical study the exposure to metabolite was decreased by 46% on day 1 to 42% on day 5.

Information for counselling of patient

Important Advices

- Abnormalities due to coagulation of blood.
- Approach to the health care provider if the patient experiences any unexpected prolonged or excessive bleeding or if bleeding time period is more.
- Adverse reactions of gastro intestine.
- Yosprala must be stopped if the signs such as coughing up blood, black, bloody stool, coffee grounds like vomiting, severe nausea, vomiting and stomach pain.
- The use of alcohol leads to bleeding.
- Renal Failure
- The kidney problems leads to change in urination must be reported to health care provider.
- Gastric Malignancy
- After completing of yosprala treatment if the symptoms of gastric ulcers still noticed Return to the healthcare provider for further treatment.
- Acute Interstitial Nephritis
- If the patient experience signs of acute interstitial nephritis Suggest to the healthcare provider.
- Diarrhea associated with Clostridium difficile.
- If the patient experience diarrhea inform to the health care provider.
- Bone Fracture - Fractures such as spine, wrist and hip must be reported to the health care provider.
- Cutaneous and Systemic Lupus Erythematosus
- Healthcare provider must be immediately reported if a patient experience Cutaneous or systemic lupus Erythematosus.
- Inform to their health care provider if liver problems are developed such as skin and eyes which appear yellowish, abdominal pain and swelling, itchy skin, dark urine color.
- Deficiency of Vitamin B-12 (Cyanocobalamin) occurs if yosprala is taken for longer than3years.So; report it to health care provider.
- Deficiency of magnesium leads to Hypomagnesaemia, if yosprala is taken continuously at least for 3months.so, report it to the health care provider.
- Toxicity of fetus leads to the Fetal Toxicity in pregnant ladies.

- Aware the pregnant women about the usage of yosprala and other NSAIDs during 30 gestational weeks which may lead to the risk of fetal ductus arteriosus in premature closure fetus.
- Yosprala should be avoided during Lactation or avoid breast feeding during the treatment with yosprala.
- Yosprala and NSAIDs under alkaline conditions leads to reversible infertility which are potential reproductive.

Pharmacodynamics

Aspirin which acts as anti-platelet agent affects aggregation of platelets by inhibiting irreversibly prostaglandin cyclo-oxygenase, the effect duration is depends upon the platelet life which mainly prevents the thromboxaneA2 factor formation which is an antiplatelet agent. Enzyme is not inhibited by non-acetylated Salicylates and does not have any effect on aggregation of platelets. In higher doses, aspirin inhibits reversibly the I2prostaglandin formation which acts as inhibitor of platelet aggregation and arterial vasodilator. The yosprala tablets of 325mg/40mg dose strength shows effect on intra gastric pH was determined in study conducted by 26healthy subjects given this dose of yosprala for 7days.The mean percentage mean time of intra gastric pH was determined was >4.0 and 51%.in studies on serum gastric effects which is observed in greater than 200 patients, the serum gastric levels were increased during the first 1 to2 weeks of once-daily administration the therapeutic doses of omeprazole is parallel with acid secretion. There is no further increase in serum gastric occurred with if the treatment is continued. When compared to histamine H2-receptor antagonists, the produced median increases by omeprazole doses of 20 mg were higher (1.3 to 3.6 fold vs. 1.1 to 1.8 fold increase).Gastric values were returned to pretreatment levels within 1 to 2weeks after discontinuation of therapy. Gastric intestinal causes increased entero chromaffin cell hyperplasia and Chromogranin increased levels may cause negative results in diagnostic investigations for endocrine neuron tumors.

Effect of Enterochromaffin-like cell (ECL)

The people treated with omeprazole for long term the 3000 patients were subjected to gastric biopsy specimens was obtained the ECL cell hyperplasia have been increased with time. There is no case of cell carcinoid, neoplasia and dysplasia has been reported. Though, these studies are of insufficient duration and size to rule out the possible influence of long-term administration of omeprazole on the development of any Premalignant or malignant conditions.

Effects of Endocrine

The oral doses of 30mg or 40mg of Omeprazole for 2 to 4 weeks had no effect on thyroid function, carbohydrate metabolism, circulating levels of parathyroid hormone, cortical, estradiol, testosterone, prolactin, cholecystokinin or secretin.

Other Effects

- The Systemic effects in the Central Nervous System, respiratory and cardiovascular systems of omeprazole have not been known up to date.
- The single dose of omeprazole 90mg is given and demonstrated there was no effect on gastric emptying of the solid and liquid components of a test meal.
- In healthy subjects, a single intravenous dose of omeprazole (0.35 mg/kg) had no effect on intrinsic factor secretion.
- Basal or stimulated pepsin output in humans has been observed as a dose-dependent effect.
- The pepsin activity is decreased; when intragastric pH is maintained at 4.0 or above, basal pepsin output is low.

Pharmacokinetics

Absorption

Aspirin: Salicylic acid is a hydrolyzed form of Acetylsalicylic acid. The absorption rate from the gastrointestinal tract is mainly dependent upon the food presence and absence, pH of gastric mucosa and other physiological factors. In the gastrointestinal tract the enteric coated aspirin products are erratically absorbed.

- The peak concentrations of aspirin were reached at 2.5hrs for 81/40mg tablet strength of yosprala, and 4 to 4.5hrs for 325/40mg tablet strength.
- The AUC and C max of aspirin were 3mcg.hr/mL and 2.6mcg/mL for 81/40mg tablet strength and 2.9mcg/mL and 2.5mcg/mL for 325/40mg tablet strength.
- No significant accumulation of salicylic acid and acetyl salicylic acid was observed by dosing strength of 325mg/40mg yosprala tablets when compared to dosing of the first day.
- The CV% of acetylsalicylic acid pharmacokinetic parameters ranged from 17% to 96%.

Omeprazole

- The concentration of omeprazole at peak plasma was reached at 0.5hours on the first day of administration and steady state.
- The C_{max} and AUC of omeprazole drug were ranged from 880-1384 ng.hr/mL and 617 to 856 ng/mL for single dose administration of Yosprala 325 mg/40 mg tablets.
- For 7days dose of yosprala 325/40mg results in approximately 2.3 fold higher C_{max} and AUC of

omeprazole at steady state to the first day of dosing.

- The CV% variability of omeprazole pharmacokinetic parameters was high ranging from 33% to 136%.

Food Effect

Aspirin: Administration of Yosprala with 50% approximately high-fat and 800-1000 High-calorie meal in healthy subjects does not affect the extent of absorption of aspirin as measured by salicylic acid AUC and Cmax but significantly prolongs salicylic acid tmax by about 10 hours. Yosprala administration before 60 minutes of a high fat or high calorie meal has no effect on salicylic acid, AUCs, C_{max} and t_{max}.

Omeprazole: Administration of YOSPRALA with 50% high-fat approximately and 800-1000 high calories meal in healthy subjects significantly reduces the extent of Absorption of omeprazole resulting in 67% and 84% reductions of AUCs and C_{max} respectively relative to fasting conditions. Yosprala administration before 60 minutes high-fat, high calorie meal reduced both the omeprazole AUC and C_{max} by approximately 15% compare to fasting conditions

Distribution

Aspirin: It is distributed widely to all fluids and tissues in the body including the central nervous system (CNS), breast milk, and fetal tissues. The concentrations are highly found in the plasma, liver, renal cortex, heart, and lungs. The protein binding of salicylates is concentration-dependent, i.e., nonlinear. At low concentrations approximately 90% of plasma salicylates is bound to albumin while at higher concentrations about 75% is bounded.

Omeprazole: The approximately Protein binding is 95%.

Metabolism

Aspirin: Aspirin is hydrolyzed rapidly in the plasma as salicylic acid. So the levels of aspirin in plasma were undetectable within 1 to 2 hours after administer of aspirin the half-life was observed within 35minutes or 0.35hrs.In liver the aspirin is Primarily conjugated and gives to form salicyluric acid, a phenolic glucuronide, an acryl glucuronide, and many other minor metabolizers. The metabolite of salicylates are saturable and clearance of total body decreases at higher serum concentrations due to the ability limited to the liver to form both phenolic glucuronide and salicyluric acid.

Omeprazole: Omeprazole is metabolized extensively by the cytochrome P450 (CYP) system of enzyme. The major part of its metabolism is dependent on the polymorphically expressed CYP2C19, which is responsible for the hydroxyl omeprazole formation, which is a major metabolite in plasma. The part which is remaining is dependent on another specific iso form, CYP3A4, which are responsible for the omeprazole sulphone formation.

Excretion

Aspirin: The salicylic acid elimination follows zero order pharmacokinetics in relation to the plasma concentration to the drug elimination is constant. The excretion of unchanged drug by renal route elimination mainly depends upon pH of urine. As the pH of urine rises above 6.5, the clearance by renal route of free salicylate increases from 5% to greater than 80%.The following therapeutic doses are approximately excreted in urine are 10% salicylic acid, salicyluric acid 75%, phenolic acid 10% and acyl glucuronide of salicylic acid 5%. The salicylic acid Half-life is of 325mg/40mg yosprala tablets are 24hrs.

Omeprazole: The administration of buffered solution of omeprazole by single dose oral dosage the minor amount of unchanged drug was excreted by urine. The major 77%amount of the drug administered was eliminated as 6 metabolites in urine. The two were identified as carboxylic acid and hydroxyl omeprazole. The remaining dose was excreted by feces. Thus, it implies that this metabolites of omeprazole were excreted by biliary excretion. In plasma Another Three metabolites have been identified which are sulfide and sulphone derivatives of omeprazole, and hydroxyl omeprazole. These metabolites which are poor metabolizers have 15 to 20% of Asians are CYP2C19.The AUC of Omeprazole in Asian subjects was about approximately four fold by the pharmacokinetic study of single dose of 20 mg omeprazole dose, of that in Caucasians there was no antisecretory activity or observed in very little amount. The half-life of omeprazole component was one hour.

Pharmacogenomics

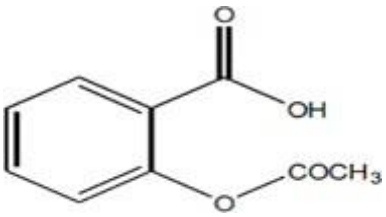
CYP2C19, a polymorphic enzyme, is involved in the metabolism of omeprazole. The CYP2C19 1 allele is fully functional while the CYP2C19 2 andCYP2C19 3 alleles are nonfunctional.

There are other alleles associated with no or reduced enzymatic function. If the patients carrying two fully functional alleles are extensive metabolizers and those carrying two loss-of-function. The poor metabolizers are Alleles. In extensive metabolizers, omeprazole is primarily metabolized by CYP2C19.

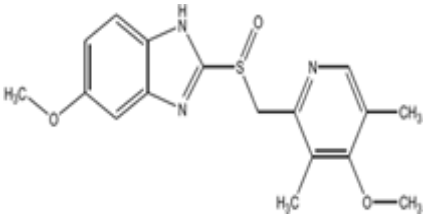
The patients' metabolism status for systemic exposure to omeprazole varies; Extensive metabolizers <Intermediate metabolizers <Poor metabolizers in approximately 3% of Caucasians.

Nonclinical toxicology

Aspirin: The administration for 68 weeks at 0.5% in the feeding of rats was not carcinogenic. In the assay of *Ames Salmonella* aspirin was not mutagenic. However, chromosome aberrations induced in cultured human fibroblasts.



Aspirin



Omeprazole

Figure 1: Chemical structure of Aspirin and omeprazole

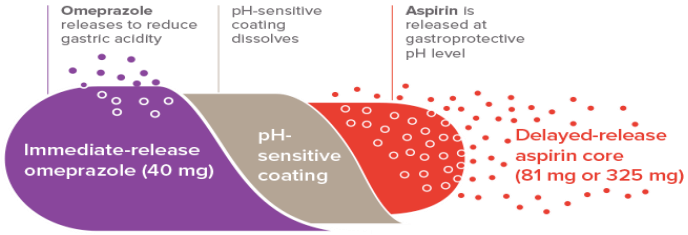


Figure 2:

Table 1:

Brand name	**Yosprala**
Generic name	Aspirin and omeprazole
Dosage form	Delayed-Release Tablets
Treatment	Ischemic stroke, Gastric Ulcer prophylaxis (Drugs.com)
Iupac name	2-acetyloxybenzoic acid; 6-methoxy-2-[(4 methoxy-3,5-dimethylpyridin-2-yl)methylsulfinyl]-1H-benzimidazole
Molecular name	$C_{26}H_{27}N_3O_7S$
Molecular weight	525.576 g/mol
Patent	6926907
Applicant	ARALEZ PHARMS

Aspirin inhibits Ovulation in rats.

Omeprazole: In 24-month two carcinogenicity studies in rats of omeprazole at daily doses of 1.7, 3.4, 13.8, 44.0 and 140.8mg/kg/day is given o.35 to 34 times daily. The human dose of omeprazole 40mg is given per day it depends upon the surface of body and produced gastric ECL carcinoid cell in related dose manner in both female and male rats, this incident effect is mainly observed in female rats, which are having higher omeprazole blood levels. In untreated rats the Gastric carcinoid seldom occurs.

In all treated groups of both sexes ECL cell hyperplasia was present. The female rats were treated with 13.8 mg omeprazole/kg/day about 3.4 times the human dose of 40 mg per day, the studies were based on surface area of body for one year, then additional year without the drug the additional year. In these rats carcinoid was not observed.

The treatment related to ECL cell hyperplasia was increased incidence observed at the end of one year was 94% treated vs10% controls. When compared to the second year the difference was very much smaller between treated and control rats was 46% vs. 26% but in the treated group showed more hyperplasia, In one rat Gastric adenocarcinoma was seen (2%). In male or female rats no similar tumor was observed. For this no strain of rat was similar tumor has been historically noted, the involved finding of only one tumor was interpreted difficultly. The toxicity was noted on 52-week in Sprague-Dawley rats, In a small number brain astrocytomas were found in males that who have received omeprazole at dose levels of 0.4, 2, and 16 mg/kg/day. In female rats no astrocytomas was observed in this study. In a 2-year carcinogenicity study in Sprague-Dawley rats, no astrocytomas were found in males and females at the high dose of 140.8 mg/kg/day about the human dose of 40mg per day 34 times based on body surface area of body. 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 when an in vitro assay of human lymphocyte chromosomal aberration was performed in one of two in vivo mouse micronucleus tests, and in bone marrow cell chromosomal aberration assay were performed In in vivo conditions. Omeprazole was negative in the *in vitro* Ames *Salmonella typhimurium* assay, an in vitro mouse lymphoma cell forward mutation assay and an in vivo rat liver DNA damage assay. Based on surface area of body

are Omeprazole when given as oral doses up to 138 mg/kg/day about 34 times the human dose of 40 mg per day, no effect was not observed on fertility and reproductive performance. A dose related significant increase in gastric carcinoid tumors and ECL cell hyperplasia was observed in 24-month carcinogenicity studies in both male and female rats.

DISCUSSION

By viewing and searching all the sources about the newly emerging drug Yosprala combination of aspirin and omeprazole, is an important drug for life threatening problem such as cardiovascular and cerebrovascular events, we could not find any analytical method so far to analyze yosprala qualitatively and quantitatively.

CONCLUSION

From the above report and study references it has been concluded that yosprala is an important drug which prevents various secondary cardiovascular and cerebrovascular events. Analytical works have been published for aspirin and omeprazole drugs individually and in combination with other drugs. Hence, it is necessary to do analytical works to analyze it either in dosage forms and bulk or in biological matrix.

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