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Pharmaceutical Sciences **Review Article……!!!**

‘‘SELEXIPAG IN THE MANAGEMENT OF PULMONARY HYPERTENSION’’

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KEYWORDS:

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ABSTRACT

Selexipag is an orally available selective IP prostacyclin-receptor agonist licensed Since 2016 for the therapy of pulmonary arterial hypertension (PAH) we aimed to Describe real-life data of patients with pulmonary hypertension (PH) treated with Selexipag we analyzed all patients initiated with selexipag from July 2016 to April 2018 at the Department of Internal Medicine V University of Munich Non-invasive and invasive parameters corresponding to the risk assessment were collected at baseline and follow-up (FU) Furthermore we recorded tolerability Twenty-six patients were treated with selexipag of whom 23 had PAH and three had chronic thromboembolic PH. At baseline most patients were in function class (FC) II or III (42% and 54% respectively) all patients were under medical treatment for PH mostly dual therapy (92%) One or more side effects were noted in 19 patients while seven reported no side-effects.

INTRODUCTION:

Pulmonary arterial hypertension (PAH) is caused by remodeling of small pulmonary vessels leading to a progressive increase in pulmonary vascular resistance (PVR) and ultimately to right ventricular (RV) failure and death the mortality risk of patients with PAH can by assessed by invasive and non-invasive parameters including World.

Health Organization functional class (WHO FC) brain natriuretic peptide (BNP) 6-min walk distance (6MWD) cardiac index (CI) and mean right atrial pressure (m-RAP) Current treatments for PAH target prostacyclin endothelin-1 and nitric oxide pathways drugs targeting each of these pathways may be combined to increase treatment effects Guidelines recommend combination therapy if initial risk is not low and escalation of therapy if risk is not low at reassessment Selexipag is the first orally available highly selective prostacyclin (IP) receptor agonist approved in the therapy of PAH in the European Union since May 2016 for patients in WHO FC II or higher The phase III trial (GRIPHON) Since its introduction to the market in 2016 selexipag has been an alternative oral therapy among both treatment-naïve patients and those with mono or dual therapy failure however limited information is available regarding the presentation and management of patients with pulmonary arterial hypertension (PAH) prior to selexipag initiation This study examined treatment patterns healthcare utilization and costs in the 12 months prior to and the 6 months following selexipag initiation.

LITERATURE REVIEW:-

A literature review was conducted to identify available evidence for selexipag and inhaled iloprost Available evidence was used to create the MCDA evidence matrix two types of documents were searched published evidence in biomedical databases and specific product evaluations for selexipag and inhaled iloprost by official healthcare evaluation bodies. Published evidence was searched in PubMed and MEDES (Medicina en Española) databases in order to answer the following search question what is the available evidence on epidemiology, health outcomes, unmet needs and economic consequences for the evaluation of drugs indicated for treatment of PAH in Spain The PICOTS (population, intervention, comparison, outcomes, time span and studies) search strategy was used the literature review in biomedical databases included published studies from 2007 to 2017. Specific product evaluations for selexipag and inhaled iloprost were searched in official European and Spanish healthcare evaluation bodies' webpages [e.g. European Medicines Agency (EMA) Spanish Medicines Agency (AEMPS) and Spanish regional and hospital evaluations all evaluations found were included regardless of the date of publication at the time of the study start the reimbursed price for selexipag had not yet been established

in Spain so a hypothetical price was used the approved list price was later used in the second phase of the study.

HISTORY:-

Selexipag sold under the brand name Uptravi is a medication developed by Actelion for the treatment of pulmonary arterial hypertension (PAH). Selexipag and its active metabolite ACT-333679 (or MRE-269 the free carboxylic acid) are agonists of the prostacyclin receptor which leads to vasodilation in the pulmonary circulation. It is taken by mouth or administered intravenously. Selexipag a selective prostacyclin IP receptor agonist is a compound discovered by Nippon Shinyaku and licensed to Actelion Pharmaceuticals Ltd outside Japan. It is licensed for the oral treatment of PAH in more than 60 countries'

The cost for Uptravi oral tablet 200 mcg is around $12,923 for a supply of 60 tablets depending on the pharmacy you visit. Prices are for cash paying customers only and are not valid with insurance plans. Uptravi is available as a brand name drug only a generic version is not yet available. The Food and Drug Administration (FDA) has approved Uptravi (selexipag) injection for intravenous (IV) use for the treatment of pulmonary arterial hypertension (PAH, WHO Group I) to delay disease progression and reduce the risk of hospitalization for PAH in adults with WHO Functional Class II-III, who are temporarily Selexipag is in a class of medications called selective nonprostanoid IP prostacyclin receptor agonists. It works by relaxing the blood vessels in the lungs to allow blood to flow easily.

PULMONARY ARTERIAL HYPERTENSION (PAH):-

PAH is a rare disorder and is characterized by the progressive obliteration of the small (50–200 μm) pulmonary arterioles due to the abnormal proliferation of all cell types within the vessel wall. This leads to an inexorable increase in the resistance to pulmonary blood flow thereby increasing right ventricular workload and ultimately causing right heart failure and death. The natural history of the untreated condition is short, with median survival varying from 1 year in scleroderma-associated PAH, 2 to 2.8 years for idiopathic PAH (IPAH), but rather longer for congenital heart disease (CHD)-associated PAH. Nonetheless, survival has More than doubled in recent cohorts now being three or more years for SScPAH4, 5 and more than 6 years for IPAH.6 it is expected to increase further when early combination therapy is adopted.

Multiple drug therapies have been developed to combat three of the dysfunctional pathways that contribute to the pathogenesis of PAH, culminating in the reduced production of prostacyclin (PGI2) and nitric oxide (NO) and the increased Production of endothelia.

SELEXIPAG PHARMACOLOGY AND PHARMACODYNAMICS:-

The development of a selective oral IP agonist was first reported in 2007, and in contrast to PGI2 and its stable analogs it was shown to have no binding activity at any other prostanoid receptor including the EP3 receptor. Selexipag is a nonprostanoid prod rug that is metabolized by the liver to an active metabolite {4-[(5, 6-diphenylpyrazin-2 yl) (isopropyl) amino] butoxy} acetic acid (ACT- 333679; MRE-269), which has a 13-fold higher affinity at the IP receptor and a half-life of around 8 hrs. ACT-333679 has limited binding affinity to EP2, EP 4, and DP1 receptors but nonetheless these receptors may contribute to immune modulatory off-target effects. With twice-daily oral administration steady state is achieved within 3 days; thus in principle this should lead to reduced side effects and convenient twice-daily oral administration. The active metabolite of selexipag was shown to induce full relaxation of rat pulmonary artery rings contracted with either ET-1 or phenylephrine, and human pulmonary arteries precontracted with PGF2α. By contrast, ACT-333679 has been reported as less effective than other prostanoids in human pulmonary arteries precontracted using phenylephrine or U46619 (thromboxane mimetic). ACT-333679 has also been shown to act as a partial agonist of the IP receptor in respect of "upstream" effects, which it has been suggested may reduce tachyphylaxis, but could also explain differences in efficacy in some models.

In the phase 1 study single ascending dose and multiple ascending dose administration were evaluated in 64 subjects. Single doses were tolerated up to 400 mg, but side effects (headache, nausea, vomiting) became frequent at higher doses45 With multiple ascending dosing 600 mg BD was tolerated and steady state was observed after 8 days with no accumulation with the half-life of the metabolite at steady state being around 12 hrs. Finally, side effects (as well as peak active metabolite concentration) were lessened by taking the drug with food. Analysis of the pharmacokinetics of selexipag and its main metabolite undertaken in the Griphon trial shows that at steady state the concentration of the main metabolite varies by 3-fold being around 10 ng/mL at trough to 30 ng/mL at peak dose effect. The bioavailability is reduced by approximately 30% in the presence of background ERAs and PDE5 inhibitors. The safety of selexipag administration has been studied in patients with hepatic and renal impairment. Selexipag metabolites are largely excreted by the hepato-biliary route after glucuronidation by UGT1A3 and UGT2B7; thus impaired liver function as anticipated affects pharmacokinetics. In this study selexipag levels were more affected by hepatic impairment than the active metabolite levels being about twice normal in moderate hepatic impairment while levels were 4–5 times normal with a significantly longer half-life in severe hepatic impairment. On the basis of PK modeling, once-daily

dosage was recommended in severe hepatic impairment (Child-Pugh C), but the usual up titration regime in other circumstances. By contrast in severe renal impairment (eGFR 15–30 mL/min), only modest changes in serum levels were observed, and while no adjustment is required caution with dose titration is recommended (if eGFR <30 mL/min/1.73 m2.

Selexipag is an inhibitor of CYP2C8 and CYP2C9 and induces CYP3A4 and CYP2C9 in vitro. Also selexipag inhibits the transporters OATP1B1, OATP1B3, OAT1, OAT3, and BCRP.

METHODS:-

I. PATIENTS

This was a multicenter, multinational, proof-of-concept, phase 2, randomized, double-blind, placebo-controlled, parallel-group trial of 17 weeks duration. Eligible patients included male or female adults (o18 yrs) with symptomatic PAH of idiopathic or hereditary origin associated with connective tissue diseases (PAH-CTD), corrected congenital heart disease (congenital systemic-to-pulmonary shunts surgically repaired o5 yrs. previously) or anorexigen use Background targeted treatment with endothelia receptor antagonists (ERAs) and/or phosphodiesterase type 5 (PDE-5) inhibitors was mandatory and patients had to have been on stable doses for 12 weeks before screening. Patients were required to have a baseline pulmonary vascular resistance (PVR) of .400 dyn? S ?cm-5, and two 6-min walk tests of 150–500 m inclusive and within ¡15% of each other Patients were excluded if they had had clinically unstable right heart failure within the last 3 months.

(World Health Organization functional class (WHO FC) IV), had received or were scheduled to receive long-term epoprostenol within 3 months of screening had a ventilation – perfusion lung scan or pulmonary angiography indicative of thromboembolic disease had evidence of left-sided heart disease or had received any investigational drug within 30 days of screening. The study was approved by the ethics committees or the study centers and was conducted according to the principles of the Declaration of Helsinki and good clinical practice. All patients gave written informed consent prior to study participation.

II. PROCEDURE

The randomization schedule 3:1 (selexipag: placebo) was computer generated by Penn Pharmaceutical Services Ltd (Tredegar, UK). Eligible patients received selexipag 200 mg twice daily (synthesized by Nippon Shinkyaku Co., Ltd, Kyoto, Japan) or matching placebo on day Dosage was then up titrated to 400 mg twice daily on day 3, to 600 mg twice daily on day 7, and to 800 mg twice daily on day 21. A slower up-titration schedule was allowed up to day 35 to allow for a maximum tolerated dose (MTD).

Although doses could be temporarily reduced after day 35 to alleviate adverse events, final dosage was required to be stable for 4 weeks prior to evaluation at week 17. As the study was blinded, investigators assessed the relationship between adverse events and study treatment before the treatment code was broken. Medical emergency was the only reason to break the codes. For each patient, treatment remained blinded until the final data for week 17 were entered and locked. After week-17 data were fixed and locked patients eligible to enter the open-label extension were unblended. For patients who discontinued prematurely or otherwise did not enter the open label extension, study treatment remained blinded until all week-17 data were cleaned and reconciled. Patients underwent right heart catheterization (RHC) at baseline and at week 17 (days 112–126 inclusive). Week 17 RHC hemodynamic assessments were conducted 4 h post-dose. Patients who withdraw prematurely or otherwise did not enter the open label extension were followed up within 30 days of their last study visit during which end-of-study assessments were performed along with echocardiography if possible. Additional hemodynamic data obtained from RHC were supported by data from secondary efficacy end-points that included established measures of clinical status in PAH patients, such as 6-min walk distance and aggravation of PAH (defined as death, transplantation, hospitalization due to worsening PAH, or aggravation of PAH symptoms, i.e. a o10% deterioration in 6-min walk distance or the need for additional PAH-specific therapies), as well as exploratory end-points, such as Borg dyspnea score WHO FC, and plasma N-terminal pro-brain natriuretic peptide (NT-proBNP) concentration The overall safety and tolerability of selexipag was evaluated in relation to the frequency of treatment-emergent adverse events and premature discontinuation of study treatment as well as change from baseline to last measurement of study.

III. STATISTICAL ANALYSIS

A sample size estimation of 44 patients was based on the assumption of a 300-dyn? S? Cm-5 difference in mean change in PVR from baseline to week 17 between treatments groups a 300-dyn? S? Cm-5 common standard deviation and a 3:1 (selexipag:-placebo) randomization ratio. Such a sample size would provide 80% power to detect a difference between selexipag and placebo based on a two-sided unpaired t-test at the 5% significance level. The primary end-point analysis was based on the per protocol (PP) set which consisted of all treated patients who did not violate the protocol in a way that might influence the evaluation of the effect of the study drug on the primary end-point. A sensitivity analysis was performed on the all-treated test which consisted of all patients who had received at least

one dose of study drug. Secondary and exploratory efficacy analyses were based on the all-treated set.

SAFETY:-

Almost all patients in both treatment groups experienced at least one adverse event, with headache, pain in jaw, pain in an extremity, nausea, and nasopharyngitis being the most frequently reported in the selexipag group. The majority of adverse events in the selexipag group were classified as mild (n55; 15.2%) or moderate (n520; 60.6%). Six (18.2%) patients in the selexipag group and four (40.0%) in the placebo groups experienced at least one serious adverse event (online supplementary table S2). Serious adverse events considered by the investigator to be at least possibly related to selexipag treatment included headache, nausea, vomiting, myalgia, and chest pain. None of the events on placebo were considered to be related to the study drug. There were no deaths Post hoc analysis showed that there was no difference in adverse events between treatment groups when stratified by background therapy, i.e. ERA or PDE-5 inhibitor monotherapy, or ERA plus PDE-5 inhibitor combination therapy. Prevalence of adverse events associated with prostacyclin analogue treatment, such as headache, pain in an extremity, pain in jaw, nausea and diarrhea, decreased over time in patients treated with selexipag No clinically relevant changes in vital signs from baseline to week 17, including blood pressure, and pulse rate, ECG parameters, including QT interval changes and laboratory tests were observed.

EFFICACY:-

At week 17, PVR (change in geometric mean expressed as a percentage of the baseline value, 95% CL) in the selexipag and placebo groups was 80.7% and 115.9% respectively this represented a statistically significant treatment effect of -30.3% (-44.7– -12.2%; Wilcoxon rank sum test p50.0045). The all-treated analysis, including all 43 patients randomized in the study, confirmed the PP analysis. Absolute values at baseline week 17 and change from baseline to week 17 for PVR are provided in online supplementary Compared with placebo, selexipag treatment seemed to be associated with a mean increase in cardiac index accompanied by a mean decrease in systemic vascular resistance (SVR), with little change in systolic or diastolic blood pressures The treatment effect on right atrial pressure appeared obscured by the decrease of the high placebo value at baseline At week 17, the mean (95% CL) change from baseline in 6-min walk distance was +24.7 (-1.6–50.9) m and +0.4 (-19.7–20.5) m in the selexipag and placebo groups, respectively One (3.0%) selexipag-treated patient and two (20.0%) placebo treated patients experienced aggravation of PAH. Five (15.6%) selexipag-treated patients experienced an improvement in WHO FC, compared with one (10.0%) placebo recipient. Two patients in each group experienced a worsening of WHO FC.

PHASE TRAIL

PHASE II

Selexipag was first evaluated in patients with PAH in a multicenter, phase II study conducted in Europe. Simonneauet enrolled 43 patients into a 17-week long randomized controlled clinical trial of selexipag vs. placebo. Patients were required to be on a stable background therapy regimen consisting of an endothelin receptor antagonist, a phosphodiesterase-5 inhibitor, or both, and to have a pulmonary vascular resistance (PVR) 5 Wood units at study entry. The primary endpoint was a change in PVR as expressed as a percentage of the baseline value. This was analyzed both in a per-protocol analysis (all treated patients who did not violate the protocol) and in an all-treated set (all patients who received at least one dose of the study drug). The PVR declined in treated patients to 81% of baseline as compared with an increase in placebo patients to 116% of baseline This difference was statistically significant with a reduction in the primary endpoint of 30.3% (selexipag vs. placebo, P0.01). Improvement compared with placebo was also seen in the cardiac index (mean 0.5 L, P0.05). Typical prostacyclin-associated side effects were reported in a majority of patients in the selexipag group including headache (most common), jaw pain, and nausea.

PHASE III

The GRIPHON clinical trial enrolled 1,156 patients with PAH into a long-term time-to-event study with a primary endpoint of morbidity and mortality.29 The main finding was a significant reduction in the composite of death from any cause or a complication of PAH (41.6% in the placebo group and 27% in the selexipag group; hazard ratio 0.60, P0.001) Improvement was also seen in the secondary endpoint of change in 6MWD at week 26 (12 m improvement vs. placebo, P=0.003) and in the exploratory endpoint of change in N-terminal probrain natriuretic peptide level at 26 weeks (treatment effect -123 ng/L, P0.001).

Enrolled patients were allowed to be treatment naïve in the event that no approved therapies were an option or could be receiving an endothelin receptor antagonist phosphodiesterase-5 inhibitor or both. Approximately 80% of enrolled patients were on one or two background PAH therapies. All patients enrolled were required to have a formal diagnosis of PAH with a mean pulmonary arterial pressure 25 mmHg PVR 5 Wood units and a pulmonary capillary wedge pressure or left ventricular end diastolic capillary wedge ressure or left ventricular end diastolic.

DOSAGE AND ADVERSE REACTION:-

Selexipag is initiated at 200 µg twice daily and increased weekly until prostacyclin-associated side effects cannot be managed or to a maximum of 1,600 µg twice daily. Prostacyclin-type side effects including headache, diarrhea, jaw pain, and nausea are common, particularly during the up-titration phase. Improvement is often seen during the maintenance phase, particularly as those who have continued symptoms can be down-titrated. Published guidelines on symptom management are lacking. Based on the common side effect profile of prostacyclin therapy, our center provides patients with recommendations for the use of acetaminophen, ondansetron, and loperamide as needed at initiation of therapy with a low threshold for the addition of tramadol for pain. We also recommend taking selexipag with food, as tolerability may be improved, but this is not required.

In the GRIPHON trial, the distribution of the final attained dosing range was 200–400 µg twice daily in 23%, 600– 1,000 µg twice daily in 31%, and 1,200–1,600 µg twice daily in 43% of patients. Interestingly, in a prespecified analysis, the efficacy of selexipag was similar in patients regardless of their stratification based on dose achieved.

Several other adverse events of special interest were also reported in the phase III clinical trial. New onset hyperthyroidism was reported in eight patients in the selexipag group (1%) and none in the placebo group (P=0.004), while anemia was reported in 8% of the selexipag group and 5% of the placebo group (P=0.05). Serial laboratory follow-up of both measures (among others) are recommended for PAH in general, 31 and no additional monitoring for patients receiving selexipag has been recommend.

CLINICAL STUDIES OF SELEXIPAG:-

A randomized, double-blind, multi-national, multi-centered, phase-2, proof-of-concept study was conducted by Simonneau et al. in 2012 (NCT 00993408) this study was assessing the efficacy and safety of the selexipag in patients with PAH. In the study of Simonneau et al. Selexipag and placebo were randomized in the proportion of 3:1 in 43 adult patients with PAH. The etiology of the PAH in the aforementioned study includes idiopathic PAH, PA related connective tissue disorder, hereditary PAH, corrected congenital heart disease or anorexigen use related PAH. Patients had been using ERA and/ or PDE-5 inhibitor during at least 12 weeks at a fixed dose. Selexipag dose had been increased from the initial dose of 200 µg twice daily to maximum tolerable dose of 800 µg twice daily in 35 days. Right cardiac catheterization had been performed at both the initiation and the end of the treatment. The geometric mean level pulmonary vascular pressure had been found as 30.3% decreased in selexipag

group compared to placebo group at the end of 17 weeks of treatment (95% CI -44.7 to -12.2%; p=0.0045). The cardiac index had also been found as significantly increased (0.41 L/min/m2, 95% 0.10-0.71) in selexipag group. Selexipag was considered as safe in terms of pharmacological effects and well tolerated.

GRIPHON study is a multi-national, multi-centered, double-blind, placebo-controlled phase-2 study (NCT01106014) and it investigates the efficacy and safety of the oral use of selexipag. It is the longest study that has been conducting about PAH. The study consists patients from 181 medical centers located in 39 countries located in North and Latin America.

Europa, Pacific Asia and Africa. Patient admission was closed in May 2013 with the final population of 1156 patients. The results of the study were reported as the biggest randomized controlled study conducted on patients with PAH. 80% of the patients had been receiving ERA, PDE-5 or a combination of these two medications for the treatment of PAH. Patients were started on selexipag treatment with the initial dose of 200 µg twice daily and the dose was gradually increased to 1600 µg twice daily. Duration of the treatment was 70.7 and 60.7 weeks for selexipag and placebo respectively.

LIMITATION:-

Have severe arrhythmias. Have decompensated cardiac failure that is not under close medical supervision. Have congenital or acquired valvular defects with clinically relevant myocardial function disorders not related to pulmonary hypertension. Are pregnant or plan to become pregnant.

ADVANTAGES:-

Selexipag is used to treat high blood pressure in the lungs (pulmonary arterial Hypertension-PAH). It is used to help slow down worsening of PAH and to decrease the chance of needing treatment in a hospital. Selexipag works by making it easier for blood to flow through the arteries in your lungs.

COCLUSION:-

Selexipag represents a major step forward in terms of designing a molecule to target a specific aspect of the prostacyclin pathway namely the IP receptor whether the is the only receptor that should be targeted is as yet unresolved. Furthermore the Griphon trial provides clear evidence of the ability of this agent to reduce disease progression at each tolerated dose in all population subgroups and in the presence of optimal background therapy.

Nevertheless this has not sorted the issue of tolerability seen with prostanoids, though the pharmacodynamics data may suggest that more frequent drug dosing could help smooth the dose – response curve and lessen side effect burden. Finally the recent long-term outcome data with

treprostinil will need to be compared carefully with the results of the Griphon trial to determine the precise clinical role of IP agonists versus other PG mimetic in the clinical armamentarium.

OUTCOME:-

A statistically significant 30.3% reduction in geometric mean pulmonary vascular resistance was observed after 17 weeks treatment with selexipaj compared with placebo (95% confidence limits -44.7--12.2; p=0.0045, Wilcoxon rank sum test) This was supported by a similar result from the all-treated set.

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