Pioglitazone Goes Out Of Use Among Indian Diabetic Population.

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ABSTRACT

The antidiabetic drug Pioglitazone belongs to the group of Glitazones having thiazolidinedione structure. Glitazones are believed to have a role in β cell protection of pancreas and help to decrease triglycerides and increase high density lipoprotein cholesterol (HDL-C). They are hepatically metabolised and hence can be used in patients with renal dysfunction. Glitazones help to reduce blood glucose and HbA1c without increasing circulating insulin. Pioglitazone was introduced in Indian market in 2001 both as single and combination products with metformin, glimepiride and alogliptin. By 2012 pioglitazone became one of the fast moving prescription drugs in the country and its sale exceeded 600 crore (6000 million) INR. The Government of India suspended the manufacture, sale and distribution of pioglitazone with immediate effect through a gazette notification on 18th June 2013 because of its association with bladder cancer. On 31\textsuperscript{st} July 2013, through another surprise notification, Government of India revoked the suspension and allowed pioglitazone to be marketed in India subject to certain conditions the manufacturers shall mention on its patient package inserts and promotional literature. By 2014 January, the sale of pioglitazone got reduced to 15-20 per cent of its sale in January 2013 in India. The study shows how drastically the incidence of pioglitazone prescriptions got reduced in the state of Kerala and highlights the need for scientific studies on Indian people.

Key words: Pioglitazone in India, Glitazones go out of prescriptions in India, Pioglitazone a controversial drug.

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INTRODUCTION

Pioglitazone was introduced to Indian market in 2001. Within a decade, it became the most widely prescribed antidiabetic drug in the country. Surprising a large section of health care professionals, patients and researchers in India, the Ministry of Health and Family Welfare, Department, Government of India, all on a sudden, suspended the manufacture, sale and distribution of pioglitazone with immediate effect through a gazette notification issued on 18th June 2013. The notification pointed out - (i) The Government of India was satisfied that the use of medicines containing pioglitazone are likely to involve risk to the people and safer alternatives to pioglitazone are available in the country. (ii) The Government was satisfied that it was necessary and expedient to regulate the way of manufacture, sale and distribution of pioglitazone in India in public interest. (iii) In exercise of the powers conferred under Section 26 A of the Drugs and Cosmetics Act 1940, the Central Government with immediate effect suspends the manufacture for sale, sale and distribution pioglitazone and all formulations containing pioglitazone in the country (Notification GSR 379. 2013).

Some of the Indian health care professionals and administrators were very much enthusiastic to advocate for pioglitazone. The advocates of pioglitazone attacked the Government decision and expressed the view that the diabetic patients in India will be adversely and seriously affected by the decision and will be compelled to use alternative therapy options which are much very much expensive.

On 31st July 2013, through yet another surprise notification, the Government of India revoked the suspension and allowed pioglitazone to be marketed in India subject to certain conditions the manufacturers shall mention on the patient package inserts and promotional literature of the drug. This notification endorsed the first and second aspects of the June 18 notifications as such and then states- “The Drugs Technical Advisory Board has examined the issue of suspension of manufacture and sale of the said drug on 19th July 2013 and has recommended that the suspension of the drug should be revoked and allowed to be marketed subject to certain conditions the manufacturers shall mention on their package insert and promotional literature of the drug” (Notification GSR 520 E. 2013). The conditions of the second notification are-

i) The drug should not be used as first line of therapy for diabetes.

ii) The manufacturers should clearly mention the following box warning in bold red letters

   a) Patients with active bladder cancer or with a history of bladder cancer and those with investigational haematuria should not receive pioglitazone.

   b) Prescribers should review the safety and efficacy of pioglitazone in individuals after 3-6 months of treatment to ensure that only patients who are deriving benefit continue to be treated.

   c) Pioglitazone should be stopped in patients who do not respond adequately to treatment (eg. reduction in glycosylated haemoglobin HbA1c).
d) Before starting pioglitazone the risk factors for development of bladder cancer should be assessed. The risk factors include age, current or past history of smoking, exposure to occupational or chemotherapy agents like cyclophosphamide or previous irradiation of the pelvic region.

e) Pioglitazone should be used with extra care in elderly patients and has to start with lowest possible dose and monitored closely because of the risk of bladder cancer and heart failure.

Both in the suspension of the drug and its re-introduction in India, the Drugs Technical Advisory Board (DTAB), the supreme authority to make such recommendations related to drugs in the country, played an important role. The main criticism regarding the two notifications is that the Indian authorities failed to conduct or promote to conduct effective scientific studies on Indian populations on various aspects of the pioglitazone since its introduction in the country.

The two notifications and the resultant discussions, deliberations, debates and the media coverage helped to make pioglitazone a popular drug in India. Pioglitazone was a favourite choice of anti-diabetic drugs to patients and physicians in India for over a decade. Now after the two notifications, the market of the drug got affected very much and the sales reduced to less than one fifth of its pre-withdrawal market share.

The destiny of pioglitazone got totally changed since June 2013 in India. When certain warning conditions were prescribed and notified for the drug, both the prescribers and those who were strongly advocating for the drug, became extra-cautious as they fear legal actions from the side of patients and the authorities in future. It is for the first time that a drug was educated to the consumers to the extent of drug information as is practiced in some developed countries like USA, Canada and Australia. Pioglitazone helped to enlighten the prescribers and dispensing pharmacists about their professional responsibilities. The practising pharmacists in the community and hospital pharmacies in India have a tough time to deal with the drug and support the prescribers with proper drug information and counselling. It also helps to make the pharmacy practice more effective and scientific in India.

**Pathophysiology and epidemiology of diabetes.**

Diabetes mellitus (DM) is one of the most common non-communicable diseases (NCDs) throughout the world. It is a heterogeneous metabolic disorder characterised by common feature of chronic hyperglycaemia with disturbance of carbohydrate, fat and protein metabolism and results from defects in insulin secretion or insulin insensitivity or both. As per American diabetes association, DM is a condition characterized by hyperglycaemia resulting from the body's inability to use blood glucose for energy.

DM is generally classified into two groups namely type 1 and type 2, though other terms like gestational diabetes are also in common use. Type 1 diabetes was earlier known as insulin dependent diabetes mellitus (IDDM), and is prevalent among children. In Type 1
diabetes the pancreas no longer makes insulin and therefore blood glucose cannot enter the cells to be used for energy. The patients have to be given insulin externally. In Type 2 diabetes which was previously known as non-insulin-dependent diabetes mellitus (NIDDM), either the pancreas does not make enough insulin or the body is unable to use insulin correctly. It affects the adult and the aged people.

It has long been known that type 2 diabetes is a disorder involving multiple components: insulin resistance, an insulin secretory defect, and an increase in hepatic glucose production. Patients with type 2 diabetes express varying degrees of these defects. Targeting insulin resistance and/or hepatic glucose production was first made possible with the introduction of metformin. About 4 per cent women develop DM due to metabolic changes during pregnancy called as gestational diabetes. Although they revert back to normal glycaemia after delivery, they are prone to develop DM later in their life.

The epidemiological analysis of diabetes provide information on several aspects like natural history, prevalence, incidence, morbidity and mortality of diabetes in populations around the world and various countries and regions. It has also led to the identification of the cause of the disease and the possible preventive measures that could be instituted to arrest or delay the onset of this disease which has reached epidemic proportions in both the developed and the developing nations (Paul z. Zimmet 1992). Prevalence of diabetes mellitus is rising all over the world due to urbanisation, aging, population growth and an increase of obesity and physical inactivity. The increase in incidence of diabetes in developing countries is due to trend of urbanization and life style changes perhaps importantly a western style diet.

As the number of patients grows across the globe, there arises stronger and more urgent need for therapeutic measures. Studies indicate that in the age group of 35-64 years, 1 out of 10 deaths are due to diabetes. Rough calculations estimate that one in every 20 deaths, is attributed to diabetes equating to 8700 deaths per day or 6 deaths every minute.

According to 2000 AD estimate of World Health Organisation (WHO), India ranked first in prevalence of diabetes with 31,705000 people (which would come to 79,441000 people by 2030) with China and USA in second and third positions. According to a recent global study on diabetes, 371 million people all over the world live with diabetes with 8.3 % prevalence and about 50 % of them remain undiagnosed. Estimated number of diabetic subjects in India in 2000 was 32 million, in 2006 was 40.9 million, in 2025 would be 69.9 million and in 2030 would be 80 million. Four out of five people with diabetes live in low and middle income countries. Half of population who die from diabetes are under the age of 60. Worldwide 3.2 million diabetes-related deaths are reported annually, a number equivalent to that of HIV/AIDS-related deaths (IDF diabetes atlas 2012).

India has a national average of 8 per cent diabetic population among adults. It is about 12 present in Bangalore and Kolkata and 10 in Delhi. State of Kerala is considered as the diabetes capital of India and has a diabetic prevalence as high as 20 per cent. The national and state drug policies of India give much attention to non-communicable diseases like DM and
many state policies help to provide anti-diabetic medicines free of cost to their people. (Mohan V 2007)

**Discovery of oral anti-diabetic Drugs.**

Even after the discovery and use of Insulin in diabetes in 1920s, it took years to get orally effective drugs approved for use in the management of diabetes. Both sulfonylurea and biguanide got introduced in the treatment of DM in the 1950s.

The use of biguanide can be traced back to the medieval times when the herb Galega officinalis was used to relieve symptoms of diabetes (Bailey C 2004). The plant was found to contain guanidine, a compound with hypoglycemic properties but too toxic for clinical use (Brunton L 2006). Two synthetic biguanides were used between 1920 and 1930 but were discontinued from clinical use because of their toxic nature. In the 1950s, three biguanides, metformin, phenformin, and buformin, were introduced. Metformin and Phenformin were introduced in the United States but were withdrawn in 1978 due to its increased incidences of lactic acidosis. In 1995, Metformin, which inhibits gluconeogenesis and improves peripheral glucose utilization, was reapproved in the United States after being in use in Europe for 20 years (Witters L 2001).

<table>
<thead>
<tr>
<th>YEAR OF INTRODUCTION</th>
<th>ANTI DIABETIC AGENT</th>
<th>PHARMACOLOGICAL CLASS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1950</td>
<td>Phenformin, Metformin, Buformin</td>
<td>Biguanides</td>
</tr>
<tr>
<td>1956</td>
<td>Tolbutamide, Acetohexamide, Chlorpropamide, Tolazamide</td>
<td>1st generation sulfonylurea</td>
</tr>
<tr>
<td>1966</td>
<td>Glibenclamide</td>
<td>2nd generation sulfonylurea</td>
</tr>
<tr>
<td>1984</td>
<td>Glipizide</td>
<td>2nd generation sulfonylurea</td>
</tr>
<tr>
<td>1990</td>
<td>Acarbose</td>
<td>Alpha glucosidase inhibitor</td>
</tr>
<tr>
<td>1994</td>
<td>Voglibose</td>
<td>Alpha glucosidase inhibitor</td>
</tr>
<tr>
<td>1995</td>
<td>Glimepiride</td>
<td>2nd generation sulfonylurea</td>
</tr>
<tr>
<td>1996</td>
<td>Miglitol</td>
<td>Alpha glucosidase inhibitor</td>
</tr>
<tr>
<td>1997</td>
<td>Troglitazone</td>
<td>Thiazolidinediones</td>
</tr>
<tr>
<td>1997</td>
<td>Repaglinide</td>
<td>Meglitinides</td>
</tr>
<tr>
<td>1998</td>
<td>Vildagliptin</td>
<td>DPP4 inhibitor</td>
</tr>
<tr>
<td>1999</td>
<td>Rosiglitazone, pioglitazone</td>
<td>Thiazolidinediones</td>
</tr>
<tr>
<td>2000</td>
<td>Nateglinide</td>
<td>Meglitinides</td>
</tr>
<tr>
<td>2005</td>
<td>Exenatide injection</td>
<td>GLP-1 agonist</td>
</tr>
<tr>
<td>2005</td>
<td>Alogliptin</td>
<td>DPP4 inhibitor</td>
</tr>
<tr>
<td>2006</td>
<td>Sitagliptin</td>
<td>DPP4 inhibitor</td>
</tr>
<tr>
<td>2009</td>
<td>Saxagliptin</td>
<td>DPP4 inhibitor</td>
</tr>
<tr>
<td>2009</td>
<td>Liraglutide</td>
<td>GLP 1 agonist</td>
</tr>
<tr>
<td>2011</td>
<td>Linagliptin</td>
<td>DPP4 inhibitor</td>
</tr>
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</table>
The hypoglycaemic activity of synthetic sulphur compounds was noted by Ruiz and his colleagues in 1937. In 1942, Janbon, a French physician, and his colleagues confirmed hypoglycaemia in patients treated with p-amino-sulfonamide-isopropylthiodiazole for typhoid. In August 1946, Lobatieres and his colleagues established that this group of drugs stimulated beta-cell release of insulin (Levin R 1984). In 1956, the first sulfonylurea, tolbutamide, was introduced commercially in Germany followed by chlorpropamide, acetohexamide, and tolaalamide, the first-generation sulfonylureas (Seltzer H 1980). In 1984, more than 14 years after their introduction in Europe, glyburide and glipizide, which are more potent second-generation sulfonylureas, became available in the United States (Kreisberg R 1985). Glimepiride, a third-generation sulfonylurea, was introduced in 1995 in the United States. The HbA1C (A1C) was decreased by 1-2%. Sulfonylureas have been in the market for more than 50 years. They are safe, cheap, and predictable, but the incidence of hypoglycemia, a major side effect, limits their use.

Glitazones as therapeutic agents for diabetes.

Chemically the glitazones are derivatives of the parent compound – thiazolidinedione. For this reason they are often included under the class thiazolidinediones which are widely abbreviated and written as ‘TZDs’. The glitazones include compounds like Ciglitazone, Rosiglitazone, Pioglitazone and Troglitazone and some experimental agents like netoglitazone and revoglitazone.

Glitazones are indicated in type 2 diabetes mellitus and are not used in type 1 diabetes. They act by activating gamma sub type of peroxisome proliferator activated receptors (PPARs) and hence are also known as peroxisome-proliferator-activated receptor agonists (PPAR agonists). They induce synthesis of genes which enhance insulin action. Glitazones increase the synthesis of certain proteins involved in fat and glucose metabolism which reduces the level of certain types of lipids and circulating free fatty acids. The glitazones increase insulin mediated glucose transport into muscles and adipose tissue and promote glucose utilization. Glitazones are believed to have a role in in β cell protection of pancreas and help to decrease triglycerides and increase high density lipoprotein cholesterol (HDL-C) (Mohsina Hyder 2013). They are hepatically metabolised and hence can be used in patients with renal dysfunction.

Glitazones help to reduce blood glucose and HbA1c without increasing circulating insulin. Some patients may not respond especially those with low baseline insulin levels to this group of medicines. More over monotherapy with glitazones as an adjunct to diet and exercise is not associated with hypoglycaemic episodes in patients. Failure of oral contraception may occur during pioglitazone therapy. In combination therapy glitazones are used along with sulfonylurea, metformin or insulin. It is also a good choice for insulin resistant cases. The diabetes prevention programme 2005 has shown that glitazones have the potential to prevent type 2 diabetes in pre-diabetics.

The glitazones were introduced in diabetic treatment in the 1990s. Right from the birth, the glitazones have had a stormy story to tell. The first one in glitazones group, ciglitazone
was developed in 1982 in Takeda chemical industries, Japan but was abandoned for marketing due to hepatotoxicity (Samraj GP 2000). Based on the studies of ciglitazone another glitazones, troglitazone was developed and studied and it was first marketed in USA in March 1997. Troglitazone reached European market in the same year and got a warm welcome. However because of liver toxicity US FDA ordered the removal of Troglitazone from their market. ) in March 2000 and it was withdrawn from the world’s market in 2000. By March 2000 Troglitazone managed to generate a sales of over $2 billion in the USA. Reports of unexpected dreadful risk of liver failure and hepatitis were published and at least 90 cases of liver failure (70 resulting in death or transplantation) were reported as associated with Troglitazone in USA (Julie NL 2008).

In May 1999, Rosiglitazone was approved by US FDA and marketed as ‘Avandia’ by Glaxo Smith Kline (GSB) whose patency expired in 2012. Pioglitazone also reached the US market in 1999 two months after the arrival of rosiglitazone. Both were approved as first line agents to be used alone or in combination with other agents (Rishi Shukla 2011). It has been marketed in the USA since 1999 and in Europe since 2000. In 2001 it got introduced in Indian market and in 2002 in France. The world wide exposure to pioglitazone was estimated to be about 20 million patient in recent times.

Rosiglitazone was withdrawn from the market of Europe by the European medicines agency in September 2010 for a possible link with myocardial infarction. In October/November 2010 it was withdrawn from Indian markets after serious discussions and deliberations extending over a period of two or three years. It was withdrawn from New Zealand in April 2011 and is still available in USA under strict restrictions. US FDA recommends two to three months checks of liver enzymes for the first year of glitazones use in diabetes to check the rare but potentially catastrophic liver complications associated with glitazones. Currently, only pioglitazone is available for use as a single agent or in combination with metformin or sulfonylurea.

Glitazones are usually used in combination with a sulphonylurea or metformin, even though it is widely used as monotherapy drug. The combination of a sulfonylurea and a glitazone appears to be logical as these agents exert opposing effects on beta cell function. The sulfonylureas focus on stimulating beta cells to secrete more insulin. Studies have shown that chronic exposure to a sulfonylurea can lead to acceleration of beta cell apoptosis, exhaustion or desensitization. The combination with metformin or a sulphonylurea should only be used in patients unable to tolerate metformin and sulphonylurea or in whom either metformin or a sulphonylurea is contra-indicated. In such cases, the glitzone should replace such drug which is poorly tolerated or contra-indicated. Glitazone plus metformin is a useful combination for obese patients. The introduction of a glitazone may adversely affect blood glucose control temporarily when used in combination therapy. Glitazones can be considered with insulin therapy in patients who have previously had a marked glucose-lowering response to glitazone therapy or in those on high-dose insulin therapies and whose blood glucose is inadequately controlled.
Pioglitazone and Takeda Pharmaceuticals.

Currently Pioglitazone is the only glitazone in use. It is used to improve glycaemic control in adults over the age of 18 with type 2 diabetes. Pioglitazone is used in monotherapy as an adjunct to diet and exercise and in combination therapy with a sulfonylurea, metformin, or insulin. Pioglitazone is marketed as trademarks ‘Actos’ in the USA, Canada, UK and Germany. In Europe it is marketed as ‘Glustin’ and as ‘Zactos’ in Mexico. In 2008, ‘Actos’ was the tenth-best selling drug in the U.S. with sales exceeding $2.4 billion. Pioglitazone is experimentally used to treat non-alcoholic steatohepatitis (fatty liver) and is also found to reduce the risk of conversion from pre-diabetes to diabetes mellitus type 2 by 72 per cent.

Pioglitazone lowers serum triglyceride level and raises HDL level without much change in LDL level. Beyond the effects on glucose metabolism, pioglitazone also has positive effects on lipid metabolism, blood pressure, endothelial function, and adiponectin and C-reactive protein levels. These make pioglitazone treatment effective beyond glucose control. Pioglitazone generally has been viewed as a safer option for patients who warrant treatment with a thiazolidinedione-class drug.

Takeda Pharmaceuticals was founded on June 12, 1781 and was incorporated on January 29, 1925. Takeda first entered the U.S. pharmaceutical market in 1977 by developing a joint venture with Abbott Laboratories called TAP Pharmaceuticals. Through TAP Pharmaceuticals, Takeda and Abbott launched Lupron (leuprolide) in 1985 and Prevacid (lansoprazole) in 1995. Pioglitazone was first marketed as ‘Actos’ in the USA by Takeda Pharmaceuticals in 1999. The US-FDA approved Actos in 1999 and in August 2012 they announced approval for its generic version. ‘Actos’ became the world’s best-selling diabetes treatment with sales peaking between March 2010 and March 2011 at $4.5 billion, or 27 per cent of Takeda revenue. Main in house sales regions of Takeda situates in Japan, US, Europe and Asia. In Japan, US, Europe and Asia pioglitazone is available as ‘Actos’ and as ‘Glustin’ in Europe and ‘Zactos’ in Mexico.

In June 2011, the FDA issued Drug Safety Alert warning that the use of Actos for more than one year may be associated with an increased risk of bladder cancer. According to a recent report issued by the Judicial Panel on Multi District Litigation (MDL) there are nearly 2,700 cases currently on file against Takeda Pharmaceuticals, the manufacturer of Actos. Plaintiffs allege that individuals who use Actos face an increased risk of developing bladder cancer and that the manufacturers concealed their knowledge of this risk and failed to provide adequate warnings to consumers and health care community.

Popularization of Pioglitazone in India

Pioglitazone was marketed from 2001 in India as a single drug as well as in combinations with other drugs such as metformin, glimepiride and alogliptin. Certain studies estimated Pioglitazone and its combinations were accounting for over Rs. 600 crore in the Indian drug
Pioglitazone combination obtained a bigger market than plain pioglitazone itself and more than 30 firms were marketing it. Pioglitazone became one among the widely prescribed drug among doctors to treat diabetes. Pioglitazone lowers serum triglyceride level and raises HDL level without much change in LDL level.

The top selling brands of pioglitazone in India included ‘DiaVista’ (Dr. Reddy’s), Pioz (USV), Pioglit (SUN), ‘Gлизон’ (Zydus Cadila) Pioglar (Ranbaxy), K-Pio (Blue cross), G-Tase (Unichem), Path (Lupin) and Piodart (BIOCON). Pioglitazone—metformin combinations were used by patients who are inadequately controlled on metformin monotherapy. Brands like Glucornorm-P (Lupin), Glyciphage –P (Franco-Indian), K-PIO-M (Blue cross), Pioglar-M (Ranbaxy), Pioglit MF (SUN), and Piodart –MF (BIOCON) were popular brands for such combinations. The price of 15mg pioglitazone tablet varied from Rs 1.30 to 6.50 in India depending on the brands. (See Table No2).

<table>
<thead>
<tr>
<th>BRAND NAME</th>
<th>MANUFACTURER</th>
<th>PRICE PER TABLET (Rs)</th>
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<tbody>
<tr>
<td>DiaVista tab</td>
<td>Dr. Reddys</td>
<td>2.30</td>
</tr>
<tr>
<td>Pioz tab</td>
<td>USV</td>
<td>5.0</td>
</tr>
<tr>
<td>Pioglit tab</td>
<td>Sun Pharma</td>
<td>1.80</td>
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<tr>
<td>Pioglar tab</td>
<td>Ranbaxy</td>
<td>6.50</td>
</tr>
<tr>
<td>k-pio tab</td>
<td>Blue cross</td>
<td>1.30</td>
</tr>
<tr>
<td>G-Tase tab</td>
<td>Unichem</td>
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<td>Path tab</td>
<td>Lupin</td>
<td>2.00</td>
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<tr>
<td>Piodart tab</td>
<td>Biocon</td>
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<td>Glizone tab</td>
<td>Zydus</td>
<td>3.48</td>
</tr>
<tr>
<td>Prepar tab</td>
<td>Glenmark</td>
<td>2.27</td>
</tr>
</tbody>
</table>

Taking the price variation among brands of different class of oral hypoglycaemic agents, pioglitazone is least costly compared to second generation sulfonylureas, meglitinides, Alpha-glucosidase inhibitors and newer class of gliptins. Pioglitazone was used for some off label indications like cerebrovascular diseases associated with impaired glucose, Diabetes mellitus type 2 – disorders of cardiovascular system (secondary disease), Diabetic nephropathy in type 2 diabetes, Generalized artherosclerosis, Poly cystic ovary syndrome and in the prophylaxis of restenotic lesion of coronary artery. Pioglitazone should not be used during pregnancy.

Adverse effects and withdrawal of Glitazones.

The safety of all new medicines could not be established as the manufacturing firms claim or indicates based on the data obtained during clinical trials or studies. Before a new drug is introduced into the market, it undergoes rigorous series of clinical trials, but often limited to the use of a maximum of 3000 patients. Hence adverse effects occurring one in 5000 or 10000 people may not be detected at the time of marketing but only when the drug
is used more widely through post marketing surveillance. If a drug can increase the incidence of a disease like myocardial infarction, the effect will only be detected by appropriately designed large trials or epidemiological studies.

Since their discovery, Glitazones are considered as a non dependent violent group among other oral hypoglycaemic agents. The life span or market life of Troglitazone was just 3 years from 1997 to 2000 and was withdrawn on grounds of hepatotoxicity. Rosiglitazone’s life span was 11 years from 1999 to 2010 and was withdrawn on grounds of myocardial infarction. In July 2010, the health ministry of India Ordered Glaxo-smithkline to suspend human studies being conducted in 19 sites across India and subsequently in October 2010, the drug controller general of India proposed to the health ministry to ban rosiglitazone. Till then diabetic drugs containing rosiglitazone were considered when diabetics could not be controlled using either of the first line choice medications- metformin and sulphonylurea. Since 2010, the only drug under the Class glitazones in popular use in India is Pioglitazone.

An important side effect of all glitazones is water retention leading to oedema. Studies have found that it is affecting only about 5% of patients using them. However it is big problem for some with significant water retention leading to a de-compensation of potential previously unrecognised heart failure. Therefore, glitazones should be prescribed with both caution and patient warnings about the potential for water retention or weight gain, especially in patients with decreased ventricular function, grade III or IV heart failure.

Up to 75% of the increase in body weight in patients taking pioglitazone is from water retention. Other possible mechanisms for weight gain include fat cell proliferation, decreased glycosuria and increased appetite (Fonseca V 2003). To minimize this weight gain, several studies throughout the world have advocated pioglitazone and metformin combination therapy (Schernthaner G 2004). An estimated a weight gain of 3.9 kg was occurred over 24 weeks in pioglitazone treated patients due to an increase in fat mass measured by dual energy x ray absorptiometry (Smith et al 2005). In contrast, a finding that a 3.1 kg increase in weight on pioglitazone was primarily due to a 2.4 litres increase in total body water (Basu et al 2006). Pioglitazone increases body weight and BMI and therefore it should not be indiscriminately used in high doses. To avoid excess weight gain, dose regulated pharmacologic interventions; extensive life style changes and proper health education are required.

The strong association with bladder cancer is hypothesized to be as a result of hyper-insulinemia where by elevated insulin levels in type 2 diabetes stimulate insulin receptors on neoplastic cells, promoting cancer growth and division (Yoshimura R 2003, Giovannucci E 2010). Exogenous insulin and other glucose lowering medications such as sulfonylureas metformin and glitazones may further modify the risk of bladder cancer.

As per studies so far, rate of bladder cancer increases with dosage and duration of use and was highest in patients treated with pioglitazone for more than 24 months and in those with a cumulative dosage exceeding 28000 mg. This study was supported by the Canadian institutes of health research and Canadian foundation for innovation.
Table 3. Reduction in Pioglitazone prescriptions in Hospital and Community Pharmacies in Kerala

<table>
<thead>
<tr>
<th>Name of District</th>
<th>2013 January Community</th>
<th>2013 January Hospitals</th>
<th>2014 January Community</th>
<th>2014 January Hospitals</th>
</tr>
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<td>Thiruvananthapuram</td>
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<td>4250</td>
<td>410</td>
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</tbody>
</table>

A randomized clinical trial (prospective pioglitazone clinical trial in macro vascular events; the PRO active study) evaluated pioglitazone with a mean follow up of 34.5 months (Dormandy J 2005). Fourteen cases of bladder cancer were observed in the pioglitazone group (0.5 %) while it was six in the placebo group (0.2%). Three studies reported a higher risk of bladder cancer among men than among women exposed to glitazones (Lewis JD 2011, Tseng CH 2011). Neumann and colleagues reported the incidence of bladder cancer per 100,000 person years, standardised to the world population, as 14.6 among men and 2.0 among women (Neumann A 2012).

Pioglitazone is well tolerated. Oral time to peak concentration is within 2 hours. Serious adverse effects of pioglitazone includes congestive heart failure, liver failure, diabetic macular oedema, malignant tumour of urinary bladder, pneumonia etc. Ketoconazole inhibits metabolism of pioglitazone. Elimination half-life for pioglitazone is 16 to 24 hours but slightly longer in elderly. Adult dose for type 2 diabetes – initial, 15 to 30 mg orally once daily which is titrated to effect. Maximum 45mg daily as monotherapy or in combination with a sulfonyl urea, metformin or insulin.

In June 9, 2011, the French Agency for the Safety of Health Products decided to withdraw pioglitazone in regards to high risk of bladder cancer. This was based on the results of an epidemiological study conducted by the French national health insurance. According to the results of the epidemiological study, French agency found that patients who are taking pioglitazone for a long time to aid type 2 diabetes significantly increased risk of bladder cancer compared to other Oral hypoglycaemic agents.

In August 2011, the US food and drug administration updated the label to warn against starting pioglitazone in patients who have active bladder cancer and to use caution if starting pioglitazone in patients with a prior history of the cancer. It is currently sold with black box warning in US and approved combination of pioglitazone with alogliptin for restricted use.

Sale of Pioglitazone- Kerala based study

Pioglitazone was withdrawn from Indian markets by June-July 2013 based on grounds of bladder cancer, but reintroduced August 2013 with certain specific label and other literature instructions. The two notifications changed the destiny of pioglitazone in the country. We have conducted a study on pioglitazone use in the state of Kerala covering both
Community pharmacies and hospitals. Both pioglitazone as a single drug and its combinations were considered for the study.

Selected 980 community pharmacists spreading across the 14 districts of Kerala were utilised for the study. Out of the 980 community pharmacists, 800 were members of the Kerala Private Pharmacists Association and the remaining 180 were owned by qualified pharmacists. It is found that the average sale of pioglitazone got reduced to 25% in the community pharmacies in Kerala at the semi urban and urban centres in January 2014 compared to January 2013.

Out of the pioglitazone prescriptions produced before the community pharmacies, 35% were old ones originated before the notifications. Two northern districts of the state, Kasargode and Kannur have highest number of prescriptions for the drug which is about 40% compared to the 2013 January situations. In districts like Wayanad and Alappuzha, the sale has reduced to about 10% compared to pre-notification period.

The situation is totally different in the Hospitals in the state. When 28 hospitals of medium and large scale (private and government) hospitals covering five districts were studied, it is noted that physicians in such hospitals have almost stopped prescription writing of Pioglitazone for diabetic patients in the state. The incidence of writing new prescriptions for pioglitazone was 4250 in January 2013 in Trivandrum which got reduced to a mere 24 in 2014 January. In Calicut 4350 became 38 while in Malappuram 2100 became 20. Ernakulam and Trissur also showed the same trend. If still pioglitazone is prescribed in Kerala, it is mainly by the rural doctors and doctors who are not aware of the controversies going on.

**CONCLUSION**

Pioglitazone is an effective and useful anti-diabetes drug with a unique insulin-sensitizing action. Compared to some other oral antidiabetic drugs, it is more cost effective. The clinical use of pioglitazone is currently under scrutiny because of certain suspected safety issues and availability of newer drugs. It has to be used judiciously and prudently with the support of rational prescription writing and professional dispensing. There is an urgent need to conduct scientific research studies on Pioglitazone in India. Physicians should recognize the early signs and symptoms of bladder cancer in patients treated with pioglitazone.

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