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Editorial

The regulatory quest for specific drugs marketed in India and western world-perception difference

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1. Theme

The availability of drugs is based on country requirement and regulatory evaluation of medicines for the community. The need may also be disease prevalence and cost based. About 344 banned FDC (Fixed dose combinations) in India in 2016, and in 2023, additional 14 FDCs have been banned. The banned drugs included those used for treating common infections, cough and fever ie combinations such as Nimesulide + Paracetamol dispersible tablets. Analgesic such as Nimesulide is not approved by US FDA, so is pioglitazone, but Pioglitazone was reintroduced in India, similarly Furazolidone is not approved by Canadian Health Authorities. Metamizole (Analgin) is not available in most advanced countries, Amphetamines, are still used in US as Over the counter drugs for short term use as anti obesity agents and in ADHD (Attention deficit/hyperactivity disorder), observed in 13% of boys and 6% of girls, banned in India, due to their addiction potential, and raised blood pressure as side effects. Phenylpropanolamine (PPA) in diet aids to the risk of hemorrhagic stroke, the Food and Drug Administration has stopped marketing products that contain PPA in 2005.

2. The Paradigm of India and the Western World

Nimesulide induced hepatitis and Acute Liver Failure with significant increase in Liver enzymes reported in many Individual Case Safety Reports in patients clinically treated for pyrexia and inflammatory disorders and the drug was never encouraged to see market face in countries like the UK, Canada, New Zealand, Australia and Denmark. and even in US, in pediatric and adult population. There is an associated risk of hepatotoxicity, a 2012 evaluation by the European Medicines Agency (EMA) concluded that the overall benefit/risk profile of nimesulide is favourable and in line with that of the other NSAIDs provided that the duration of use is limited to not more than 2 weeks. In India and in 50 countries, Nimesulide 100mg, is still widely available but caution is to be exercised in cases of suspected or known liver disease. Since 10 March 2011 Nimesulide formulations are not used for children below 12 years of age. Fixed dose combination of Nimesulide and Paracetamol has recently banned as a weaning process of irrational drug combination. Similarly the triple combination of Nimesulide and paracetamol with serratiopeptidase, Nimesulide + Tizanidine, Nimesulide + Dicyclomine, Nimesulide + Paracetamol + Levocetrizine + Phenylephrine + Caffeine have been discontinued. Nimesulide for adult use, now stand the test of time in Indian market, although global sales in market are increasing.

The U.S. Food and Drug Administration (FDA) categorizes Actos (Pioglitazone) for more than one year

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may be associated with an increased risk of bladder cancer. Pioglitazone is withdrawn in certain countries such as France and Germany. India has a very low prevalence of reported overall and bladder cancer–specific pioglitazone-related ADRs compared to Europe and the America. Possible explanations for the difference in reporting rates include variance in genetic makeup. In India, pioglitazone is used more often as triple drug combination instead of dual drug therapy with metformin and at lower doses compared to UK.

Association between incidence of bladder cancer and pioglitazone use was not seen in Indian studies. In a cohort study of 252,467 patients aged ≥40 years from the Kaiser Permanente Northern California Diabetes Registry, it was concluded that no clear evidence of an association between use of pioglitazone and risk of the bladder cancers was observed.

Indian drug regulatory authorities withdrew pioglitazone in June 2013 but then revoked the ban due to lack of sufficient evidence and recommendation by the Drug Technical Advisory Board (DTAB). Pioglitazone is marketed with warning, where in patients who present with symptoms such as nausea, vomiting, loss of appetite, pain in the upper right part of the stomach, flu-like symptoms, dark urine, yellowing of the skin or eyes, unusual bleeding or bruising, or lack of energy, should discontinue drug soon and should seek advice of their physician.

Fenfluramine, is approved as a Schedule IV controlled substance, by US FDA for the treatment of seizures associated with Dravet syndrome (Life threatening, chronic form of epilepsy) only in patients age 2 and older.

Both drugs Fenfluramine (Restricted use) and Phentermine are available in US, but withdrawn from domestic Indian market. Weight loss can increase cardiovascular risk associated with obesity. Phentermine hydrochloride (HCl), a sympathomimetic appetite-suppressant approved in the US for short-term (up to 12 weeks) treatment of obesity in conjunction with dietary and lifestyle modifications. The drug comes under Schedule IV drug under the Convention on Psychotropic Substances in US. In UK drug was withdrawn in 2000 and also in India, due to cardiovascular side effects, such as rise in BP and heart rate.

Phenylpropanolamine used in cold and cough remedies is freely available in India. However it was banned in North America and Western Europe some years ago. Global phenylpropanolamine market is vast.

3. Market Dynamics

Regulatory process in most countries are different and drugs are approved as per the need of the population, similarly withdrawal is done as per the incidences of adverse drug reactions in exposed population. Genetics, dose, dosage forms are other factors which ensure marketability of drug in country. Propoxyphene combinations (Banned in EU in 2009 and US 2010) were available as pain relivers and 2013 withdrawn in India. Regulatory withdrawal is based on observations as what the other regulators do in their country. This is under policy of global observance. Oxyphenbutazone is marketed within India, though not available in US, as there is justification that low dose range is used within India. Test for the regulators in India, will be to track more signals for adverse drug reactions before they cast their vote against Nimesulide (nearly 264 brands) and Pioglitazone (65 major brands) and pioglitazone combinations (with Metformin, Metformin and Glimepiride, Vildagliptin, Linagliptin, SGL2 inhibitors) which are freely marketed in Indian market.

4. Conflict of Interest

None.

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