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Review on Ban Drug-Nimesulide

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ABSTRACT:
The Aim of present work is to record Nimesulide a Nonsteroildal Anti Inflammatory Drug is being sold as over the counter drug has to banned absolutely due to prevalence of Nimesulide brought on acute hepatitis. On February 12, 2011, the Union Ministry of Health and Family Welfare subsequently had determined to droop the pediatric use of the Nimesulide suspension. From 10 March 2011 Nimesulide formulations are now not indicated for human use in children below 12 years of age. On September 13, 2011 Madras High Court revoked a suspension on manufacture and sale of pediatric drugs Nimesulide and phenylpropanolamine (PPA). Though the authorities of India has banned the pediatric use of Nimesulide for frequent fever and ache due to its negative effects on the liver, its usage by using adults is being expanded daily without any prescription. The drug was once banned in 2000 in various countries like Switzerland, Spain, United states etc, whereas in India it was banned in 2011 which was once too late to be banned and nonetheless handy in India for person use notwithstanding of its hepatotoxicity and viable drug interactions.

Keywords: Adverse Drug Reaction, hepatotoxicity, Nonsteroildal Anti Inflammatory Drugs, pain, banned drugs, Regulatory bodies, unapproved drugs.

I. INTRODUCTION:

Nimesulide, (4 nitro 2 phenoxyphenyl) methanesulplfonamide is a non steroidal anti-inflammatory drug (NSAID) with relative specificity for COX-2 that is no longer available in the United States, however is being used broadly in other nations in the remedy of acute pain. Nimesulide has been linked to a low price of transient serum enzyme elevations throughout therapy, however also to many cases of clinically apparent acute liver injury that can be extreme and can result in acute liver failure, need for emergency liver transplantation and death. Nimesulide is reachable as tablets, granules, suppositories, oral suspensions, drops and topical gels.Original Nimesulide is marketed in extra than 50 countries on the whole Europe, central and Latin America and Asia. The approved alternate names are Ainex, Aulin, Donulide, Eskaflam, Heu-gan, Mesulid, Nexen, Nimed, Nimedex, Nisulid and Scaflam. According to the summary of product characteristics (2003) Nimesulide is approved for use in the cure of acute pain, in the symptomatic cure of painful osteoarthritis and in primary dysmenorrhea. Nimesulide has been marketed in France on account that 1998, is neither extra wonderful nor better tolerated than different NSAIDs. Many reports and evaluations published by way of drug regulatory companies in Spain, Ireland and Italy have warned of the hepatic unfavorable outcomes of Nimesulide.

Pharmacology of Nimesulide:[1,2]

Nimesulide is a sulfonanilide compound with anti- inflammatory properties. Its pharmacological profile (better inhibition of PG synthesis in inflammatory areas than in gastric mucosa), advised that it may be a selective inhibitor of COX-2. In countless invitro assays using both purified COX-2 and COX-1 preparations or cell preparations (both from animal and human origins) expressing COX-1 or COX-2, ten out of eleven exceptional groups have proven that Nimesulide selectively inhibits COX-2. The COX-2/ COX-1 inhibitory ratio varies, according to the assay preparation, from about 0.76 to 0.0004 i.e. a 1.3 to 2,512 fold greater selectivity for COX-2 than for COX-1. Moreover, an invivo entire blood assay performed on wholesome volunteers demonstrated a widespread fall in COX-2 PGE2 production without any impact on COX-1 TXB2 production in topics handled with Nimesulide (100mg b.i.d. for 2 weeks) versus no impact on COX-2 PGE2 and an almost total suppression of COX-1 TXB2 in subjects treated with aspirin (300mg t.i.d. for two weeks). Nimesulide can as a consequence be regarded a noticeably selective COX-2 inhibitor. At the endorsed dosage of 100mg b.i.d., it is as fantastic an analgesic and anti-

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inflammatory agent as classical NSAIDs, and a well- tolerated drug with few side-effects according to large- scale open research and a world assessment of a giant number of managed and non-controlled comparative trials.

Nimesulide is a NSAID with appropriate anti-inflammatory, analgesic and antipyretic things to do anticipated of such compounds. However, in addition it has some special therapeutic and pharmacological activities. The novel therapeutic aspects include a distinctly low toxicity to the gastrointestinal tract and kidneys, it can be given to most sufferers who ride respiratory troubles with other NSAIDs, and the onset of analgesia is comparatively quick. The foremost novel pharmacological actions received using Nimesulide invivo at therapeutic doses, or invitro at concentrations inside the therapeutic range of free (unbound) drug, include: a preferential inhibition of prostaglandin synthesis by means of COX-2, and reductions in cytokine action/release, histamine release, the release of enzymes that degrade cartilage, and the release of superoxide anions and different poisonous substances from neutrophils. Interactions with different pills are few and of little or no medical significance.

Ban of Nimesulide:

The Nimesulide prompted toxicity and its severity lead to liver transplantation occasionally death. The instances reported all through the world made the drug to get ban in many nations completely, the regulatory bodies involved in ban of the drug had been given in table 1. But in some countries like India the drug is partly banned and also reachable as over the counter remedy for adult use. No pharmacist warns the patient about possible interactions and drug brought on toxicity so fover the counter medications, as if they are troubled solely about their sales and business. The inspectors also no longer bothered to enquire about over the counter medicine records. The Indian authorities introduced ban on the drug in 2011 for pediatric usage where as the drug is available for grownup use in existing day Indian market. The general procedure concerned in ban of a drug in India is given in Figure 1.

The customers are purchasing the drug from pharmacies due to lack of know-how on drug interactions and drug induced hepatotoxicity, which are responsible to motive severe consequences once in a while loss of life. A list of agents and the drug mode of interactions are given in Table 2 [1]

List of Combinations Banned by Ministory of Health and Family Welfare:[3]

Combination of Nimesulide and Diclofenac Combination of Nimesulide, Certizine and Caffeine Combination of Nimesulide andTizanidine Combination of Nimesulide and Paracetamol dispersible tablets Combination of Nimesulide and Serratiopeptidase Combination of Nimesulide, Pitofenone, Fenpiverinium and Benzyl alcohol Combination of Nimesulide and Dicyclomine.

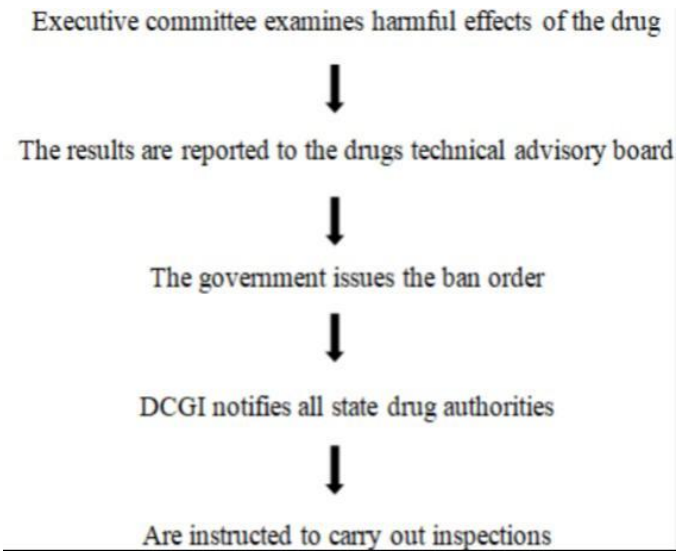

Figure 1: The general procedure involved in ban of a drug

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Abbreviations	Regulatory Bodies	Countries
FDA	Food and drug administration	United States
EMEA	European Medicines Agency	
TGA	Therapeutics Good and Administration	Australia
CDSCO	Central Drugs Standards Control Organization	India
SIDC	State Institute For Drugs and Control	Czech Republic
NAM	National Agency for Medicines	Finland
BfArM	Federal Institute For Drugs and Medical Devices	Germany
PCHRD	Philippine Council For Health Research and Development	Philippines
SIDC	State Institute For Drug Control	Slovak Republic
MPA	Medical Products Agency	Sweden

Table 1:Regulatory bodies involved in specific ban of Nimesulide.

Acts and Sections:

Drugs like Nimesulide, Rofecoxib, Phenylpropanamine and others are banned based totally on Section 26a of Drugs and Cosmetics Act 1940 through the Ministry of Health and family welfare, in India, after change of the Drugs Act in 1982, the Government has acquired the energy to prohibit manufacture and sale of sure capsules and irrational 19 FDCs.

Sr.N	Agent	Mode of interaction
1.	Anticoagulants	Nimesulide increases the risk of bleeding when taken with anticoagulants.
2.	Beta-blockers	Nimesulide may diminish the antihypertensive effects of these drugs.
3.	Angiotensin converting enzyme inhibitors	Nimesulide may diminish the antihypertensive effects of these drugs.
4.	Digoxin	Nimesulide may increase serum concentrations of digoxin.
5.	Loop diuretics	Nimesulide may reduce the effectiveness of these diuretics and may increase serum concentrations of potassium
6.	Potassium sparing diuretics	Nimesulide may reduce the effectiveness of these diuretics and may increase serum concentrations of potassium

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7.	Penicillamine	Nimesulide may increase the bioavailability of penicillamine
8.	Methotrexate	Nimesulide may increase serum concentrations of methotrexate

Table 2: List of agents and the drug mode of interactions.[1]

CASES REPORTED:

1. Case from India:[4]

A 6 year old boy.who was suffering from fever for 4 days for which he was treated with Nimesulide (without prescription) for 4 days before coming to doctor. On examination, patient was found with jaundice and haematuria

1a. Laboratory studies of the child were as follows:

When the LFT report comes. bilirubin total - 8.8mg/dl and bilirubin direct 5.2mg/dl. SGOT, SGPT and alkaline phosphate were 587IU and 2932IU, respectively. Liver function test after 9th day from withdrawal of Nimesulide showed bilirubin 1.34mg/dl and bilirubin direct 0.81mg/dl. SGOT, SGPT and alkaline phosphate were 98.48IU and 189.6IU and 1603IU, respectively. these parameters of liver function showed significant improvement after withdrawing Nimesulide. Complete blood count report Hb-11.2g/dl.TLC-9300µl, PCV-34%, RBC count-4.2mn/mm3 MCH-26.67pg, MCV-80.95 fl, MCHC-32.94%, Platelets-261 103 /µl, bleeding time and clotting time (BTCT)were normal (bleeding time-3'36" minute, clotting time 6'13" minute), while prothrombin time index: PTI test 13sec, PTI-92% was also within the normal limits. On first day the urine was dark yellow colour, albumin bile salt and bile pigments were also detected. Microscopy shows the presence of pus cells 2-3/HPF, RBCs-40 to 50/HPF. A repeat examination of urine, at a different pathological laboratory confirms. urine culture was found to be sterile after 24hrs of aerobic incubation. Repeating this test on 9th day of the Nimesulide withdrawal shows a normal urine sample.

Serotological test for hepatitis A, B, C and E viruses, were found negative. This eliminates the other common causes of hepatitis.

The pediatrician stopped the use of Nimesulide and managed the child conservatively on outpatient basis. The child improved subsequently without any specific intervention.

The pediatrician stops the use of Nimesulide on children's, due to its chronic effects on liver functioning.

2. Case filed in Saudi Arabia:[5]

The objective is to report the occurrence of Nimesulide induced acute hepatitis confirmed by biopsy and an in vitro lymphocyte toxicity. A 54 year old women treaded with Nimesulide for chronic low back pain was admitted to the hospital, the biopsy report confirms that she was suffering from acute hepatitis. Her liver functioning test result where returned to normal within one month after Nimesulide discontinuation and an invitro lymphocyte toxicity confirmed that the liver injury was due to Nimesulide induce due to excess consumption of Nimesulide. These effects are might be reversible on discontinuation of the drug, but occasionally can progress to fatal hepatic failure upon longer usage.

2b. Affiliated by Department of Gastroenterology, Nahariya Hospital, B. Rappaport Faculty of Medicine, Technion, Israel.

2c. Case reported by N krivoy, Mshiller, R farah, H I cohen, Lstruminger, Rreshef. In 2001 September.

3. Case file for acute liver failure attributed to Nimesulide London England:[6]

A 58 year old woman feel uneasy 10 days after starting Nimesulide for chronic back pain. She was seen and found to have mild elevations in serum enzymes, She continued using Nimesulide, but she developed further symptoms including nausea and then she stopped using it after two weeks, she noted dark urine, jaundice and shortly she was admitted to the hospital because of chronic symptoms. She had no history of liver disease, alcohol abuse or risk factors for viral hepatitis. She had taken Nimesulide for short periods in the past. Her other medications included birth control pills which she had taken for 6 years and sertraline which she had taken for 11 months. On admission, she was acutely ill with jaundice and confused Laboratory results shows a total bilirubin of 16.9mg/dL, ALT 1046 U/L, AST 386 U/L, alkaline phosphates 114 U/L, GGT 112 U/L, albumin 2.8 g/dL and INR greater than 12. Tests for hepatitis A, B, C, E BV and CMV were negative. She had low titers of ANA (1:25). Abdominal ultrasound showed normal liver, spleen and biliary ventilation. She developed progressive hepatic failure and went into emergency liver transplantation within 3 days

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of admission, but had primary graft non function, multiorgan failure and died within a day of the surgery. Auto biopsy report shows massive hepatic necrosis.

3a. It was found in lancet (londan, England) in 1999 Jan 2. By P A McCormick, F Kennedy, M Curry, O Traynor.

4. Case reported in France:[7]

A 49 year old women was treated with Nimesulide for 3 days. She was admitted in intensive care unit for acute liver failure which effects the functioning of the brain due to its toxicity, hepatic support by molecular absorbant recirculating system (MARS) was performed, hepatic transplantation was done within 12hours of admission it shows a rapid improvement and gets discharged with in 4 days of transplantation. Nimesulide induce hepatic toxicity is inpredictable and it shows different symptoms. cinical symptoms are progressive, delaying in the treatment. Case draws attention to the risk of hepatic failure due to the treatment with Nimesulide which leads to hepatic transplantation or death.

4a. Affiliation- department of anesthesia reanimathion, pavillon reanimation, hospital Edouard Herriot in France.

4b. Case reported by - F Christin, D HayiSlayman, J JBaillon, C-E Ber, B Delafosse, J Dumortier, T Rimmele. case reported on 27th September 2008.

5. Case reported in spain:[8]

A 63 year old women who was treated for 7 months with Nimesulide (100mg/b.i.d) for symptomatic osteoarthritis. the patient was admitted to hospital with the clinical picture of progressive jaundice for 3 weeks. Clinical and analytical studies shows acute liver failure, this is confirmed by liver biopsy, which showed submassive necrosis. Serological test for different viral agents causing hepatitis were all negative. She shows severe haemolytic anemia in resistant to several treatments and needed multiple transfusions. After 23 days of admission. the patient shows hepatic effects on functioning of brain and received an orthotopic liver transplant on 25th day of admission. the improvement after transplantation was good and the patient continues in good health with no evidence of haemolys is with in 2 years.

Affiliation gastroenterology service hospital universitario central de Asturias, Oviedo, spain.

6. Case reported in Southern Brazil:[9]

Department of Clinical Medicine, University Hospital, Universidade Estadual de Londrina (UEL), Londrina. An 81years old women who was treated with Nimesulide for 6 days with hematesmesis (blood in vomiting) and epistaxis (nose bleeding) before 2 days of hospitalization.

Clinical examination shows extensive coagulation disorder (bleeding), diffuse hemeatomas, hypotension and tachypnea (abnormal rapid breathing). Laboratory tests shows Abnormalities in coagulation test, leukocytosis, reduce platelets, hemoglobin, Red Blood Cells count, high direct bilirubin, serum aspartate transaminase (AST) gamma glutanyl transpepridase (GGT) Alkaline phosphate and renal function biomarkers. test of hepatitis B and C were not reactive. Carcino embryonic antigen (CEA) cancer antigens (CA19-9 and CA-125) levels were increased by 1,000 to 10,000 and 13 fold.but the Alpha fetoprotein level was normal.

This indicates that a malignant tumor in the bile duct was not originated from liver. after 36 hours of hospitalization the patient's condition become worst and leads to death. The autopsy finds that includes acute hepatitis with hepatocellular collapse, as well as metastasis of a carcinoma from the bile duct.

The necropsy findings included liver acute hepatitis with inflammatory infiltrate, coagulative necrosis and hepatocellular collapse (Figure 2). Moreover, there was metastasis of moderately differentiated carcinoma, probably from the bile duct (Figure 3).

Carcinoembryonic antigen (CEA) and CA-19-9 levels were increased, respectively, by 1,000 and 10,000-fold. CA-125 was slightly increased (13-fold) and alphafetoprotein (AFP) levels were normal (Table 3).

- Nimesulide may have contributed in the fatal liver failure without the affect of carcinoma presented by the patient. Precautions are required in prescribing Nimesulide for liver disease in patients.

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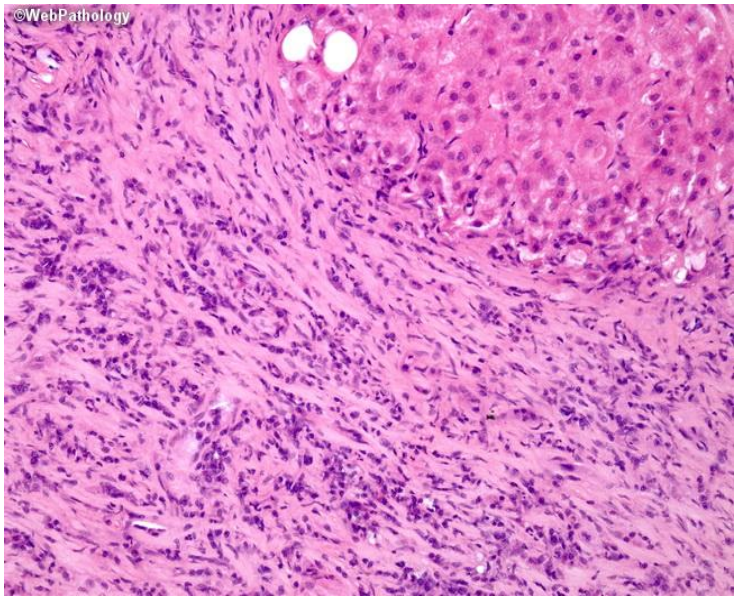

Figure 2. Histopathological features of the liver, focusing on acute liver failure: acute hepatitis with hepatocellular collapse in the patient's liver. The arrows show extensive areas of coagulative necrosis and inflammatory infiltrate (hematoxylin and eosin stain; original magnification X 20).[9]

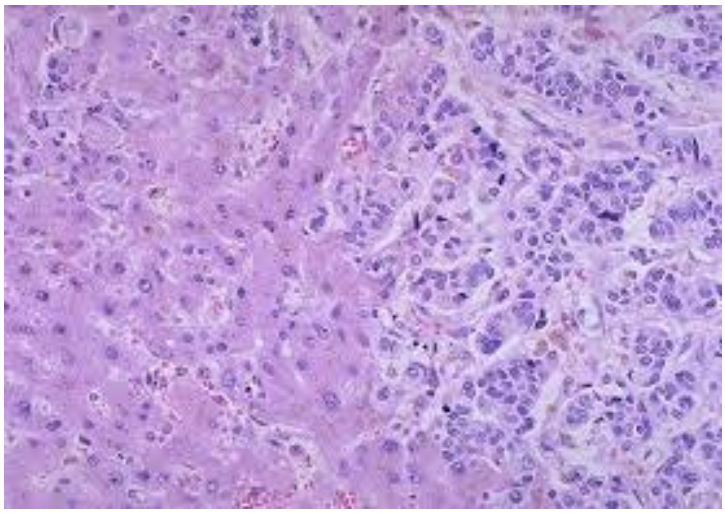

Figure 3: Histopathological features of the liver, focusing on adeno carcinoma metastasis: adeno carcinoma metastasis, probably originating from the bile duct, in the patient's liver. The arrows show the neoplastic cells (hematoxylin and eosin stain; original magnification X 40).[9]

	REFERENCE VALUE	**VALUE**
Hepatitis C	NR	NR
Hepatitis B (HBsAg)	NR	NR
CEA	< 3 ng/ml	1,224.35
CA-19-9	< 37 U/ml	10,079.97
CA-125	< 35 U/ml	476.4
AFP	< 8 ng/ml	7.49

Table 3: Hepatitis and cancer biomarker tests.[9]

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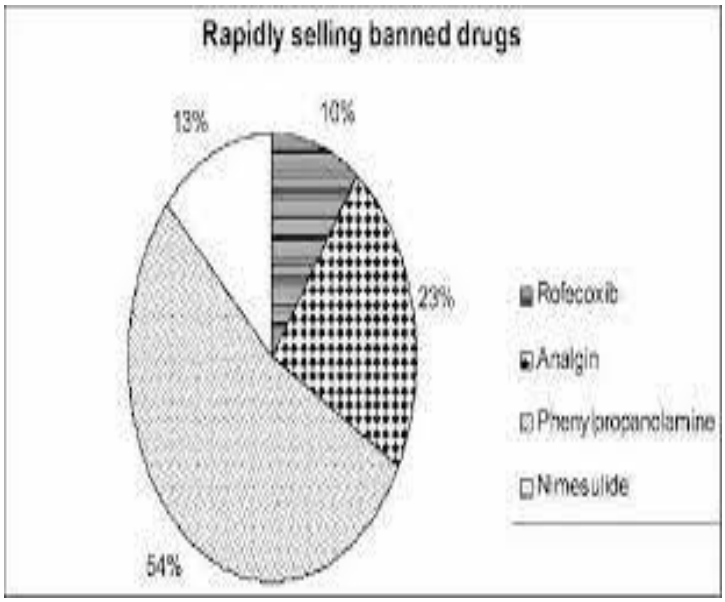
Different Nimesulide Brands Present in Indian Market:

1. NISE Tablet (manufactured by Dr. Reddy's Laboratories, Ltd. composition Nimesulide 100mg). Nise Tablet is a pain relieving medicine. It is used for treatment of inflammatory condition including joint disorders such as Rheumatoid arthritis, postoperative painful condition, fever, and period pain. Nise Tablet should be taken with food. This will prevent you from getting an upset stomach. In general, you should try to use the smallest amount necessary to control your symptoms, for the shortest possible time. You should take this medicine regularly while you need it. Try not to miss doses as this will make the medicine less effective. It is used as pain relief, fever.

2. NIMREST 100MG TABLET (manufactured by Ranbaxy Laboratories Ltd, It consist of-Nimesulide). Nimrest 100 MG Tablet is a non-selective non-steroidal anti-inflammatory drug (NSAID) which is used as a second-line therapy to treat acute pain associated with osteoarthritis and menstruation. It is also used to treat mild to moderate pain caused due to sprains and strains of joints and muscles. This medicine is not recommended for use in patients below 12 years of age.

Availability of Banned Drug in India:

World wide tragedies like Jake leg paralysis, Thalidomide sealed limbs and Elixer Sulfanilamide are warning humans not to prefer self medications. Taking medications that are prescribed with the aid of physicians helps to avoid possible drug interactions and negative drug reactions. The over the counter medications are being responsible for negative consequences like hepatotoxicity, renal failure, cardiac failure, extreme pores and skin reactions, GI toxicity, coronary artery insufficiency etc. Banned tablets like Phenyl Propanolamine, Analgin, Cisapride, Nimesulideetc are being sold in market. Cisapride an antacid drug reasons coronary heart abnormality, Phenylpropanolamine used in cough syrups will increase the risk of strokes, Sibutramine an urge for food suppressant used in treatment of obesity, is related with elevated danger of coronary heart attacks. Nimesulide an Non steroidal anti-inflammatory drug is hepatotoxic which leads to liver transplantation or every now and then death. Though the Indian government in 2011 introduced a late ban on Nimesulide for pediatric use, however it is nevertheless being used for adults as over the counter medication.



Due to the cases said in adults on Nimesulide induced Hepatotoxicity and drug interactions, it was once banned in international locations like United states, Ireland, Spain, Finland, Belgium etc. The drug found in Switzerland where it was never used. The drug which has to be banned actually, is nevertheless being used in India as Over the counter remedy regardless of of its negative effects and possible drug interactions.

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The World Health Organization in the year 2008 has listed Nimesulide in "Consolidated List of Products whose Consumption and/or Sale have been Banned, Withdrawn, Severely Restricted or Not Approved via Governments" beneath Pharmaceuticals: Restrictions in use and availability.[11]

II. CONCLUSION:

Several reviews and reviews made via drug regulatory agencies of Spain, Ireland and Italy have warn for hepatic adverse results of Nimesulide. In Europe the database of European pharmacovigilance shows that Nimesulide is related with more cases of severe liver damage. The dose of Nimesulide use was recommended in the summary of product traits (SPC). Liver damage takes place within 15 days after the first dose of Nimesulide in one 1/3 cases. Nimesulide was once ban in many international locations like Switzerland, spain, Ireland, Finland and united states. The drug which has to be banned actually, is nevertheless being used in India as Over the counter medication in spite of of its damaging effects and possible drug interactions. There are many drugs which are to be banned are reachable in Indian market, and had been being sold as over the counter medicinal drugs illegally besides warning the patients about negative drug reactions and drug interactions, which making the unaware customers to suffer.

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