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The list of prohibited drugs

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Abstract

Medicines are essential part of health care system and they are regulated and cleared off by various regulatory commission and authorities for clear and safety use of drug in a society. The fixed dose combination can provide much better clinical outcome in management of disease especially in case of chronic diseases like hypertension. This is usually produced by the enhancement of medication adherence in the patient during a medication regimen The central Government on 10th March 2016 through a notification in the Gazette of India, prohibited 344 Fixed dose Combinations under section 26 A of the Drugs and Cosmetic Act, 1940.The different fixed dose combination that are banned are briefly explained along with the rationale for the banning of the drug. It was concluded with the need to ensure that the ban on irrational FDCs should not be taken in a wrong context. A logical long-term solution should be taken to prevent future failure in regulating irrational drugs. This can only be enhanced with hand in hand collaboration of all the involving people including the public to enhance national progress. This progress can help in rational healthcare system putting foundation towards development of the country.

Keywords: prohibited drugs, drugs in India, medication, fixed dose combination, regulatory authority, irrational drugs

Introduction

Medicines are essential part of health care system and they are regulated and cleared off by various regulatory commission and authorities for clear and safety use of drug in a society. In India, The Ministry of Health and Family Welfare regulates the manufacture, sale or distribution for human use of drugs. A combination drug or a fixed dose combination is a drug that is a single dosage form with two or more active pharmaceutical ingredients.

The fixed dose combination can provide much better clinical outcome in management of disease especially in case of chronic diseases like hypertension. This is usually produced by the enhancement of medication adherence in the patient during a medication regimen. A study shows 24%-26% reduction of non- compliance with right prescription pattern (1) Even when these fixed dose combination has major positive sides, the irrational drug combination can pose harm to the patient which in turn cause issue for fundamentals of Indian healthcare system. The regulatory ban of irrational drugs can enhance the regulatory architecture and patient safety mechanisms. This ban can be based on various studies including drug profile assessment, post-marketing surveillance. One largely populated country like India, the over exploitation of fixed dose combination drugs are common. This is due to regulatory agencies lapses, irrational pharmaceutical policies, irrational medical practice of prescribers and pharmacists, ignorance of patients through irrational or non-prescription based self- medications. Another reason for the ban of irrational fixed dose combination is to reduce the antimicrobial resistance which is one of another raising concern.

The central Government on 10th March 2016 through a notification in the Gazette of India, prohibited 344 Fixed dose Combinations under section 26 A of the Drugs and Cosmetic Act, 1940. The prohibition was based the recommendation that suggest of therapeutic non-justification of active pharmaceutical ingredients. They also suggest that these drugs may also involve risk to human beings. DTAB, Drug Technical Advisory Board furnished the report on these drugs and given to Central Government. This report was then studied and 328 FDCs in the country.

Fixed dose Combination of Aceclofenac and paracetamol and Rabeprazole [(2)]

Aceclofenac and Paracetamol belongs to Anti-inflammatory agent that work by inhibiting or lowering the pain and inflammation pathway. Rabeprazole act as a protective agent for the gastric irritation caused by Aceclofenac. The prohibited combination of strength 100mgand 325 mgand10 mg in enteric coated tablet. The dosing interval of three drugs are different as Acelofenac is twice daily, paracetamol is thrice daily and rabeprazole is once daily. This implicates the pharmacokinetic incompatibility. The FDC is not approved anywhere in the world. The literature regarding safety and efficacy of this combination is not available in Pubmed & Google scholar. (2)

Fixed dose Combination of Nimesulide and Diclofenac [(2)]

The prohibited dose of strength 100 mgand 50 mg are in soft gelatin capsules dosage form.(2)

They are prohibited due to: Nimesulide in combination form has potential of misuse and have safety concern documented. No additional advantage but hepatotoxic potential of nimesulide and adverse effects add up. Pharmacodynamically irrational FDC as both have same mechanism of action (both drugs acting on the same enzyme). Thus, combining two NSAIDs does not and

cannot improve the efficacy of treatment. These can add up the cost and adverse effect.

Fixed dose Combination of Nimesulide and Cetirizine and Caffeine [2]
The strength of the fixed dose combination is 100 mg and 5 mg and15 mg in the dosage form of Tablet was prohibited because of the nimesulide in combination has potential of misuse in indications for allergic conditions as well as it has documented safety concerns.

Fixed Dose Combination of Nimesulide and Tizanidine [2]
The strength of the fixed dose combination of Nimesulide and Tizanidine is 100 mg and 2 mg of Tablet dosage form was prohibited due to the potential of misuse as well as safety concerns in regard with Nimesulide. There is different dosing schedule for these drug combination

Fixed dose Combination of Paracetamol and Cetirizine and Caffeine [2]
The strength 500 mg and 5 mg and 15mg Tablet was prohibited because of pharmacokinetic incompatibility as dosing interval vary for paracetamol as well for cetirizine as both are TDS/QID and OD/BD. The prohibition was also supported by the fact that no trial evidence could be found in PUBMED and Google scholar. The important safety debate concerning multi-ingredient, multi-symptom relief products for common cold and flu is that they commonly contain paracetamol and that users may not be aware of this may accidentally overdose when they take multigradient product with other medicines also containing paracetamol.(3)

Fixed Dose Combination of Diclofenac and Tramadol and Chlorzoxazone [2]
Diclofenac sodium IP and Tramadol HCL BP and Chlorzoxazone USP of strength 50mgand37.5mgand 250 mg in film coated tablet form because of the liability of tramadol to be abused as it is an opioid analgesic with which combination can cause additive sedation.

Fixed Dose Combination of Dicyclomine and Paracetamol and Domperidone [2]
The fixed dose of 20 mg and 500 mgand10 mg in an uncoated bilayer tablets was prohibited due to its pharmacodynamic irreverence as each ingredient has different therapeutic use and can lead to misuse and toxicity. Combining can lead to dangerous elevation of the body temperature.

Fixed Dose Combination of Nimesulide and Paracetamol Dispersible Tablets [2]
The dose of 100mg/100mgand500 mg/325 mg as dispersible tablets or uncoated tablets is prohibited with the reasoning that as a dispersible dosage form it has a potential of misuse in children. There are safety concerns with paracetamol and Nimesuilide. The Combination is also not approved.

Fixed Dose Combination of Paracetamol and Phenylephrine and Caffeine [2]
Dose of 500mgand10mgand32 mg oral tablets are prohibited because they are pharmacokinetically irrelevant and misuse and overuse of one ingredient of Fdc in case it is not indicated

Fixed Dose Combination of Diclofenac and tramadol and Paracetamol [2]
The fixed dose of 50mgand 37.5 mgand325 mg in film coated tablets as tramadol is itself a potent opioid analgesic. FDA is not rational as addition of Paracetamol and Diclofenac will not provide any additional benefit

Fixed dose Combination of Diclofenac and Paracetamol and Chlorzoxazone and Famotidine [2]
The fixed dose of 50 mgand 325 mgand 250 mgand 20 mg in tablet form as Pharmacodynamically irrelevant as each ingredient has different dosing schedule / dosing requirement. This can lead to misuse and toxicity.

Fixed Dose Combination of Nimesulide and Serratiopeptidase [2]
The fixed dose of 15 mgand 100 mg in tablet form is prohibited because of safety concern as well as lack of evidence for efficacy of serratiopeptidase over nimesulide.

Fixed dose Combination of Paracetamol and Diclofenac and Famotidine [2]
The fixed dose of 500mgand 50 mg and 20 mg as film coated tablets as it is pharmacodynamically irrelevant as each ingredient has different therapeutic use and FDC will lead to misuse. The paracetamol dose is high. Both the diclofenac and paracetamol hepatotoxic. There is a point of concern of importance regarding safety of multiple active pharmaceutical ingredients for common cold and flu. This can lead to overdosage of paracetamol in patients unaware of the composition of the drug.

Fixed Dose Combination of Nimesulide and Pitofenone and Fenpiverinium and Benzyl Alcohol
The 100mgand2mgand0.02mgand4.0% v/v Injection as there is no evidences on safety and efficacy of the FDC. Safety concerns with Nestlike

Fixed Dose Combination OF 3 tablets of Serratiopeptidase (enteric-coated 20000 units) IP and Diclofenac potassium bp and 2 tablets of Doxyocyline HCL IP.
The strength of the fixed-dose combination is 10 mg and 50 mg and100 mg in the dosage form of KIT was prohibited because
It will lead to antibiotic resistance. Documented efficacy of Serratia peptidase not available. May lead to misuse. Do not offer any particular advantage over the individual drugs. on the other hand, the patient is exposed to a greyer risk of gastrointestinal (GI) irritation and serious bleeding from unsuspected peptic ulceration. [2]

Fixed Dose Combination of 3 tablets of Paracetamol IP and Dextromethorphan Hydrobromide IP and Phenylephrine HCL IP and Chlorpheniramine Maleate IP.
The strength of the fixed-dose combination is 325 mgand 15 mg and05 mg and 2 mg in the dosage form of Tablets was prohibited because
Dosing schedule is incompatible. Ingredients will aggravate the adverse effects of sedation and drowsiness and also will interfere with the reflexes. Centrally acting anti-tussive not

to be combined with the anti-histamine drug. Paracetamol dose is subtherapeutic. [2]

Fixed Dose Combination of 3 Tablets of Omeprazole Magnesium USP eq. to Omeprazole and Paracetamol IP and Diclofenac Potassium.

The strength of the fixed-dose combination is 10 mgand 500 mg and50 mg in the dosage form of Tablets was prohibited because Pharmacodynamic irrelevant as each ingredient has different therapeutic use and FDC will lead to misuse. Paracetamol dose is high. Both diclofenac and Paracetamol hepatotoxic.An important safety debate concerning multi-ingredient, multi-symptom relief products for common cold and flu is that they commonly contain paracetamol (acetaminophen) and that users who may not be aware of this may accidentally overdose when they take the multi-ingredient product with other medicines also containing paracetamol. (2)

Fixed Dose Combination OF 3 tablets Nimesuide BP and Paracetamol ip and Phenylephirine HCL IP and Cetirizine HCL IP and Caffeine IP.

The strength of the fixed-dose combination is 100mgand 325mg and5 mg and 25mg in the dosage form of Uncoated Tablets was prohibited because Nemisulide combination has the potential of misuse in indications for allergic and accidentally overdose when they take the multi-ingredient product with other medicines also containing paracetamol. There is pharmacokinetic incompatibility among the drugs. Nimesulide has documented safety concerns. Hepatotoxic potential of both the drugs.

Fixed Dose Combination OF 3 tablets Diclofenac Sodium ip and Paracetamol IP & inactive Polyethylene Glycol 400 USNF and Lignocaine HCL IP and Benzyl Alcohol IP and (preservative) and sodium metabisulphate IP

The strength of the fixed-dose combination is 25mgand 75mg & 565.53mg 10mg 1.0% w/v and 1mg in the dosage form of injection was prohibited because

Lignocaine with a causal hypersensitivity reaction. DICLOFENAC SODIUM 50mg capsules relieve pain, minimize swelling and ease inflammation in prerequisites affecting the joints, muscle groups, and tendons including Rheumatoid arthritis, osteoarthritis, acute gout

Fixed Dose Combination of tablets Salbutamol andCholine Theophylinate andAmbroxol

The Oral liquid dosage form was prohibited of dose 1 mg and50mgand15 mg. This is prohibited because of the reasoning regarding the pharmacodynamic and misusing index. The current scientific understanding shows that this fixed-dose combination is pharmacodynamically irrelevant. That is, it may show irrelevant effects in the patient consuming this fixed-dose combination. Another reasoning states that the mucolytic agents can't be used with anti-asthmatic drugs. This is because it is liable to be misused as expected. This can also lead to unnecessary patients' exposure to the drug and its adverse impacts.

Fixed Dose Combination OF 4 tablets Ambroxol and Salbutamol and Choline Theophyllinate and Menthol

Choline Theophyllinate and Salbutamol are used in the medical treatment of Asthma. Salbutamol is a beta 2 adrenergic agonist used as a bronchodilator. It works by relaxing the muscles in the airways and widens the airways. A choline salt of theophylline, also called oxtriphylline, has an action of the mechanism by directly relaxing the smooth muscle of the bronchial airway and pulmonary blood vessels. Thereby it relieves bronchospasm and thus the vital capacity is increased. This can also act to produce stimulation of the cardiac skeletal muscle. Ambroxol is a mucolytic that thins and loosens phlegm and facilitates the cough out. It acts by breaking down the acid mucopolysaccharide fibers. This in turn makes the sputum thinner and less viscous. Therefore promotes mucus clearance. It also stimulates the synthesis and release of surfactant type II pneumocytes.

Fixed Dose Combination OF 4 tablets Oflaxacin and beclomethasone and clotrimazole and lignocaine HCL

The strength of the fixed-dose combination is 0.3%and. 025% and1% and2% in the dosage form of Drops was prohibited because

Pharmacodynamically irrelevant-Each ingredient of FDC has different therapeutic indication and is at variance from the concept and purpose of FDC. Combining antibiotic, antifungal, steroid in the present FDC is liable to be misuse and emergence of resistance and adverse effects. Use of steroids in case of fungal infection might actually worsen the treatment as it encourages fungal growth. No study is found supporting the combined use of antibacterial with an antifungal ingredient.

Fixed Dose Combination of 2 tablets Omidazole and Oflaxacin

The strength of the fixed-dose combination is 125mgand 50mg in the dosage form of Suspension /Oral liquid was prohibited because

Both ingredient of the FDC have different therapeutic indications. Inappropriate use of ornidazole will lead to emergence of antibiotic of antibiotic resistance against quinolones

Fixed Dose Combination OF 3 film-coated tablet of Paracetamol and Psedoephdrine and Cetrizine Dihydrochloroide

Fixed volume composite definition strength is 325mg 30mg 10mg film coating tablets. It was banned because Paracetamol interval is TDS/QID and is cetirizine OD/BD, so pharmacokinetic incompatibility, can't find a trial in PUBMED and Google scholars.

An important safety controversy regarding the common cold and flu multi-component, multi-symptom relief products generally contain paracetamol (acetaminophen), which users who are unaware of this fact take the multi-component. It means that you can sometimes accidentally overdose. Product with other drugs including paracetamol.

Fixed Dose Combination OF 2 % Injection Phenylbuta zone and sodium salicylate

The strength of the fixed-dose combination tablet is 200mgand 20mg in the dosage form of Injection was prohibited because safety has not been established and FDC is at risk of toxicity. The combination of two drugs that act on the same enzyme also has no synergistic effect. Therefore, combining the two NSAIDs does not improve the

therapeutic effect. It increases the cost of treatment and, more importantly, the side effects. Human use is already banned domestically.

Fixed Dose Combination of 2 uncoated tablets Nimesulide BP and Serratiopeptidase IP.

The strength of the fixed-dose combination is 100 mg and the 15 mg uncoated tablet dosage form is prohibited because The strength of the fixed volume combination is 100 mg 15 mg in the uncoated tablet dosage form.

The rationale for prohibition were Mestle Reed safety issue. There is no evidence that serrati peptidase offers any special advantage over Nimesulide. On the other hand, patients are at increased risk of gastric (GI) irritation and severe bleeding due to unsuspecting peptic ulcer.

Fixed Dose Combination of 4 uncoated tablets paracetamol and Diclofenac potassium BPand Chlorapheniramine maleate IP and magnesium trisilicate

The strength of the fixed-dose combination is 325 mg and50mg and4 mg and 100 mg uncoated tablet dosage form is prohibited because Pharmacodynamioc Inappropriate-Each ingredient has different therapeutic uses for FDC and can lead to misuse and toxicity (liver and kidney).

Fixed Dose Combination of 5 tablets Bromohexine hydrochloride IP and Guaifenesin IP and Phenylephrine hydrochloride IP and Chlorpheniramine Maleate IP and Paracetamol IP.

The strength of the fixed-dose combination is 8mgand 100mg and5mg and 2mgand325mg in the dosage form of uncoated coated Tablets was prohibited because pharmacodynamically irrelevant combination–

Buromuhekisin: mucolytic agents that increase mucus secretion should not be administered with the priority of antihistamine and anticholinergic action in order to dry mucus secretion for anticholinergic action. Chlorpheniramine: H1 antagonists are known to reduce runny nose, The drying effect can be more harmful because it tends to cause drowsiness. The dosage of paracetamol is below the therapeutic dose, and potential abuse of FDC preparations can be liver toxicity

Fixed Dose Combination of 2 tablets Phenytoin IP and Phenobabitone sodium IP.

The strength of the fixed-dose combination is 100mg and 50mg in the dosage form of uncoated coated Tablets was prohibited because

Pharmacodynamically irrelevant-Phenobarbital affects the metabolism of the liver enzyme CYP2C9\/10, which lowers the level or effect of phenobarbital. Phenobarbital decreases the level of phenytoin by increasing metabolism. Phenobarbital may or may not change phenytoin levels (through competitive residence).

Conclusion

There was huge amount of opposition against the prohibition of fixed dose medication in India. The pharmaceutical companies and industries are meant see these regulations as a stand for better health care system. This also implicates the need for increasing the awareness of the rational drug use, not only in healthcare team but also for the pharmaceutical industries. These bans do mark an important milestone in healthcare policy in India. An appropriate measures for regular robust regulatory check is needed for further deep rooting of regulatory system in India.

The key recommendation for better adaptability after the ban can be done through various measures. This can be enhanced through building up sales strategies, rationalizing drug portfolios, marketing budget allocations in pharmaceutical companies for the banned drugs. The regulatory authority can establish better scientific documents and standards that needs to be established immediately and regularly updated. The rational medication use should be made into public awareness through behavior change communication campaigns. This can be enhanced through educational channels. The medical practitioners should be aware of the effects and should rationalize the prescription of fixed dose combinations. They should take up leadership role in spreading the awareness and to enhance better prescription behaviors, antibiotic stewardship and rational drug use to promote patient safety. It is important to ensure that the ban on irrational FDCs should not be taken in a wrong context. A logical long-term solution should be taken to prevent future failure in regulating irrational drugs.

This can only be enhanced with hand in hand collaboration of all the involving people including the public to enhance national progress. This progress can help in rational healthcare system putting foundation towards development of the country.

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