“CRITICAL ANALYSIS OF FIXED DOSE COMBINATIONS (FDCS) PRESCRIBED IN A TERTIARY CARE HOSPITAL IN VIJAYAPURA”

By

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Dissertation submitted to the

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In partial fulfillment of the requirements for the award of the degree of

DOCTOR OF MEDICINE

IN

PHARMACOLOGY

Under the Guidance of

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LIST OF ABBREVATIONS USED

FDC	Fixed Dose Combination
CDSCO	Central Drugs Standard Control Organization
ADR	Adverse Drug Reaction
API	Active Pharmacological Ingredient
TB	Tuberculosis
HTN	Hypertension
DHF	Dihydrofolate
DHFRase	DihydrofolateReductase
MIC	Minimum Inhibitory Concentration
CTZ	chemoreceptor trigger zone
BBB	blood brain barrier
HIV	human immunodeficiency virus
RBM	Roll back malaria
ACT	artemisinin combination therapy
S/P	sulfadoxine- pyrimethamine
DCGI	DCGI (Drug controller general of India)
WHO	world health organization
NSAID	non steroidalanti inflammatory drugs
DOTS	Directly Observed Treatment Shortcourse
HAART	Highly active antiretroviral therapy
ARV	Antiretroviral drug
3TC	Lamivudine

NVP	Nevirapine
d4T	Stavudine
AZT	Zidovudine
IUATLD	International Union Against Tuberculosis and Lung Disease

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INTRODUCTION

Introduction

Fixed dose combinations (FDCs) refer to "products containing two or more active drugs used in a single dosage form for a particular indication" [1].

Use of FDCs is associated with many advantages like synergistic action, reduced adverse effects, reduced pill burden, reduced cost of the treatment and improved patients compliance[2].

However, certain disadvantages like incompatible pharmacokinetics, inflexible dose ratio and increased toxicity are limiting factors.

It is well accepted fact that drugs are better to be formulated in a single dosage form. Combinations (FDCs) are

FDC is worthy when the combined active pharmacological ingredientsAPIs have proven benefits of therapeutic efficacy or safety with respect to single compound administered individually [3].

Considering better patient compliance a larger number of physicians prefer FDCs. As a result pharmaceutical companies take up this opportunity and market huge combinations that include many of irrationalcombination.

In recent years, there has been increase in irrational FDCs.

Indian laws are not strongly defined to yield approval for the sale of combination drugs by central or state drug control authorities.

Therefore, rationality of the fixed dose combinations has been a standout amongst the most disputable and problematic issue in medical practice which needs to be answered [4].

FDCs are said to be rational when they meet certain criteria such as pharmacokinetics of the API should not vary largely, API must act by different mechanisms, and should not cause supraadditive toxicity [5].

There are several disadvantages of FDCs. Titration of the dose of a drug to suit individual patient is not possible. One of the drugs in a combination may be unnecessary.

There is increased incidence of adverse effects and it is difficult to identify which drug in FDC is responsible for the adverse drug reaction ADR.

FDC has often incompatible pharmacodynamics which can mask some of the symptoms making the diagnosis and treatment of the underlying condition difficult[6].

Endorsement by Central Drugs Standard Control Organization (CDSCO) has been made compulsory for FDCs since 1961.

A few alterations to the guidelines, especially the last one in 2002, have just made it clear.

However, the extent of unapproved FDC plans did "not diminish in overall" after May 2002. Numerous unapproved FDC were accessible in India for use in different therapeutic regions, for example, analgesia, neuropsychiatry disorders and infectious diseases.

Numerous FDCs have been endorsed without clinical information of safety and efficacy. Premise on which endorsement has been allowed are not published[7].

With pharmacovigilance being at a primitive stage and low adverse event reporting, the nonappearance of data on adverse effects make it unsafe.

Therefore, the present study is undertaken to critically analyze FDCs prescribed in tertiary care hospital and to promote use of rational FDCs.

AIMS AND OBJECTIVES

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1 Drug utilization review of FDCs prescribed to the patients attending Out Patient Department of tertiary care hospital.

2 To critically analyse an FDCs using a pretested structural tool

3 To increase the awareness for use of rational FDCs.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

Fixed-dose combination (FDC) implies the inclusion of two or more active pharmacological ingredients added together in fixed doses which is then manufactured and distributed as a single dosage form. "Combination drugs", "Combination drug product" is used as synonyms for FDCs.[8]prescribing them is a routine practice.[9]

Initially developed with the aim of treating single diseases like TB, The FDCs now have splayed their use in treatment of multiple diseases. The FDCs are now been extensively and successfully used in treating conditions like HTN with associated hypercholesteraemia with the use of drugs like Caduet (Atorvastatin/amlodepine) and moderate HTN with drugs like Exforge (Amlodepine/Valsartan).

Use of FDCs dealing with multiple conditions is complex , The Probability of such conditions co-existing should be high. Only then we can find increase number of prospective patients who utilise and benefit from given FDC ,So FDCs must mainly target on those conditions which maximum co-exist in the given population.

The FDCs are produced in bulk and only by adopting the above strategy the FDCs can reach out to huge number of potentially applicable population thus justifying its manufacture, distribution and stocking.

Rationality for use of FDC

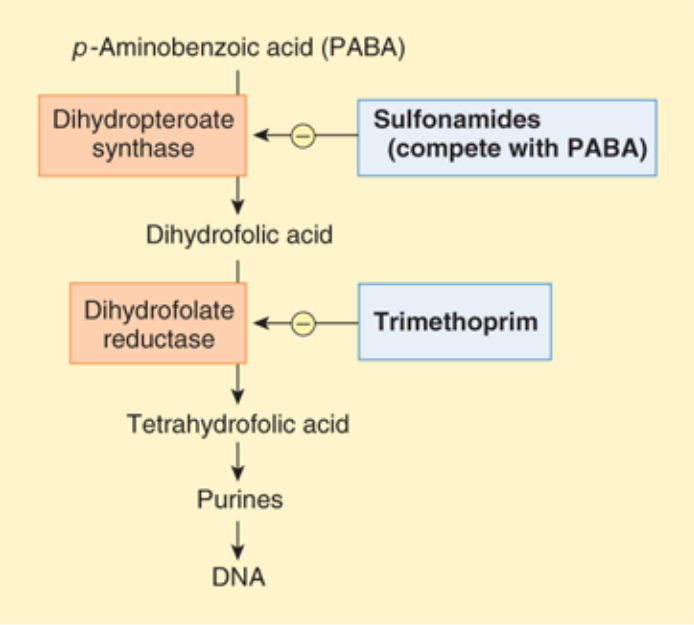
Is based upon certain merits such as

- Drugs when combined must have different mechanism of actions and yet show additive or synergistic effect.
- The pharmacokinetics of the drug in a combination should not vary widely
- The combination should not produce supradditive adverse effects of the ingredients
- **Example** :-sulfamethoxazole and trimethoprim (eg. Co-trimoxazole),Levodopa with carbidopa,[10].

Co-trimoxazole

Rational use of FDC is associated with many advantages like synergistic action and increased efficacy (eg. Co-trimoxazole), reduced adverse effects[11]

The fixed dose combination of sulfamethoxazole andtrimethoprim is called cotrimoxazole. Sulfamethoxazole inhibits DHF synthesis.Trimethoprim is a diaminopyrimidine related to the antimalarial drug pyrimethamine which selectively inhibits bacterial dihydrofolatereductase (DHFRase).[12]



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Sulfonamide and Trimethoprin when act individually is a bacteriostatic.However combination of these two drugs show bactericidal effect. When the organism shows sensitivity to both the drugs, maximum synergism is seen.

The action of the other drug overshadows when the organism shows partial sensitivity or partial resistance to any one component.

Trimethporim has advantage when combined with Sulfamethoxazole because both have nearly the same half life of approximately 10h which is one of the important criteria for combining two drugs. When sufamethoxazole and Trimethoprim were given in the dose of 5:1, and when they attained the concentration of 20:1 respectively, optimal synergy was observed. Also the MIC (Minimum Inhibitory Concentration) of each component got lowered by 3-6 times. This was because, trimethoprim having large volume of distribution, entered many tissues and attained lower plasma concentration as compared to sulfamethoxazole. Also trimethoprim was rapidly absorbed. Trimethoprin is 40% bound to plasma protein were as sufamethoxazole is 65% plasma protein bound[13]

Levodopa with carbidopa.

Levodopa is the immediate precursor of Dopamine and hence has definitive effect in Parkinsonism.

The efficacy of the drug is beyond other individual drug; however Levodopa it is inactive when administered alone. More than 95% of the drug undergoes peripheral decarboxylation. And only 1-2% of the administered drug crosses the blood brain barrier where it is converted to Dopamine.

The peripherally decarboxylated levodopa act on peripheral organs, heart, blood vessels, CTZ and lead to adverse side effects like nausea , vomiting and hypotension.

Thus to potentiate the action of levodopa and lower its side effects alongside, it is combined with the drug called Carbidopa. It is a peripheral decarboxylase inhibitor and thus inhibits the conversion of levodopa into doapamineperipheraly.

Carbidopa by itself does not cross the BBB, and allows levodopa to cross BBB

Benefits of the combination are-

1. The required dose is reduced by one fourth and half life of levodopa is increased.

2. Therapeutic levels of levodopa are achieved quickly. Adverse effects are reduced.

3. Reduced Cardiac side effects.

4. Pyridoxine reversal of levodopa does not occur.

5. "On –off" effect is reduced.

6. There is a Better improvement and improved response to levodopa.[14]

Advantages of fixed dose combination

- Convenience in dose schedule and better patient compliance.
- Enhanced effect of the combinations e.g-oestrogen +progesterone.
- Minimisation of side effects E.g-levodopa+carbidopa
- FDCs also reduce pill burden and cost of the therapy and hence better patient compliance (eg. Antitubercular drug combination) [15].
- FDC can improve compliance in the treatment of chronic infectious diseases.eg-treatment of TB and HIV.

Disadvantages

- The dose of any component cannot be adjusted independently.
- Pharmacokinetics may be widely different.
- It becomes difficult to identify one particular drug which is causing harmful/beneficial effects
- some fixed dose combinations show more adverse effects E.g-nimesulide+paracetamol.
- One of the drugs in the combination maybe wasteful- E.g- vitamin+iron
- There will be increase in price if unnecessary drugs are included. e.g-ibuprofen+paracetamol+caffeine~![16]

FDCs in India

India has been called the pharmacy of the world, the reason being numerous generic drugs that are manufactured.

Thousands of fixed dose combination (FDC) drugs- that is combination of 2 or more API in a set ratio to make a single dosage form, usually a tablet or capsule - are prepared, formulated, and sold in India. Also some of them are exported internationally.

Many FDCs are risk free and efficaciously implied in the treatment of HIV, Parkinson's, contraceptive pills, pulmonary tuberculosis and many more conditions.

Prior marketing, both active pharmacological ingredients and the doses needed are standardized and made stable.

FDCs are substantially promoted and used on a large scale within the country, for;it's a promising innovation of the National pharmaceutical industry. One can gain access to them through the pharmacies, wholesalers, dispensing doctors, and from the hospitals as well.

Problem with FDC in India

Yet, the discompose existed for years. Many fixed dose combinations that had never been approved for marketing but were given licenses to manufacturing by authorities.294 of such drugs were seized and banned by the National regulatory authorities in the year 2007[17].

FDC manufacturers disputed the ban though, and the issue is still unsettled in the court.

In the year 2012 the committee by government of India investigated the efficacy and the standards of the FDCs and issued a report highlighting the multiple problems i.e. the efficacy and the standards, including their approvals.

The committee found that the new formulations that were never approved had received manufacturing licenses by the state authorities. [18] The investigation by the committee revealed that many of the FDCs in market were not tested for safety and efficacy which in turn could put the patients at risk. Also many of FDCs were medically inessential.

'The marketing of the FDCs without approval was eased by the 'obscurities' in the rules on new drugs before the amendment of existing law in May 2002 ,' said the report. Nevertheless, no obscurities were identified in drug rules, but still many unapproved FDCs were seen in market in spite of the amendment.

Measures

Prior marketing, the drugs are subjected to rigorous testing wherein their efficacy and safety profile is tested. Despite of it, some adverse events of drugs appear only after the drug is released in the market which is further monitored by the pharmacovigilance .

Pharmacovigilance is all about detection of adverse events of the drugs, their understanding and assessment, prevention of short and long term complications of the drugs.

The approval or banning of a drug is controlled by the DCGI (Drug controller general of India). It issues the ban order to drugs that are found to have deleterious effects on health.

The entire cycle of production and sale stops evidently if there are no buyers. Certainly, the problem can be solved by doctors by simply not prescribing such drugs. And as a matter of course, the chemists stop buying and selling the drugs. And ultimately it necessitates the manufacturers to stop production and marketing those particular drugs.

The list of companies with their products that are affected by ban

S. No. Company Brand Name of Medicine

1. Alkem- Sumo, Taxim AZ
2. Glenmark- Ascoril
3. Abbott -Phensedyl, Tossex, Tribet
4. Ipca-Zerodol P
5. Cipla-Triexer&Oflox
6. Macleods-Panderum Plus
7. GSK-Crocin Cold & FLU Max
8. Mankind-Paediatric syrup T-98 TedyKoff
9. Lupin-Gluconorm
10. Medley Pharmaceuticals- O2
11. Panacea Biotech -Nimulid
12. Micro Labs -Dolo Cold
13. Wockhardt-Zedex, Ace Proxyvan
14. Pfizer-Corex
15. Sun Pharma-Gemer P, Chericof, Decoff
16. Paras Lab- D Cold-Total
17. Torque Pharma-Kofnil
18. Procter and Gamble- Vicks Action 500 Extra

Therapeutic justification should be the basis for FDCs. Each and every FDC should be clinically relevant and carefully justified (e.g., in cases where each API of the FDC has several possible dosage form, doses that were shown benefit on clinical outcomes must be preferred).

Appendix VI of Schedule Y (Drugs and Cosmetics Rules 1945) specifies the diverse requirements for approval for marketing of various FDCs. The same is further more extended to provide a detailed guidance for industry.[19]

Drug control issues in India

The efficacy, safety and bioavailability of an individual drug are likely to get changed when it is combined with other drug(s) during the manufacture of FDCs. Hence the FDCs are treated as ' new drug ' and similar to other new drugs, they will have to get approval from the Drug Controller General of India prior marketing, as per the Drugs and Cosmetic Act 1940.

As per rule 122 (E), of the Drugs and Cosmetic Rules 1945, the same criteria holds good to US market as well.

The DCGI (Drug controller general of India) had issued notifications for banning many FDCs. The principal notification under section 26- A of the Drug and Cosmetic Act 1940 (sale, prohibiting manufacture and distribution of certain FDCs without proper therapeutic justification or are most likely to involve human at risk),banned nearly 75 FDC formulations from year 1983 till date.

Some examples are, FDCs of tranquilizers and anti- inflammatory agents with vitamins etc.[20]

FDCsin other country

The aggregate production and marketing of FDC preparations vary from country to country.

In a European country like Spain, it has been up to 56%, while in Japan it has been as low as 10%.

In India, the FDC production and marketing greater than one third of total new products introduced in last decade. However, developing countries lack such statistical data. FDCs comprising iron preparations, analgesics, vitamins, antacids etc hold maximal share. [(21)].

The national list of essential medicines has 354 essential drugs and 29drug combinations.[(22)]However, the WHO lists 325 essential drugs which include 28 drug combinations.[(23)]

FDCs are very popular in the Indian drug market and have been extensively increased in the last few years.

The rationality of each and every FDCshould be based on certain criteria /guidelines such as:

The FDC is said to be rational only if following criteria are fulfilled:

• The pharmacokinetics must not be widely different

• The combination of APIs should not have supra-additive toxicity of the ingredients.

• The drugs in the combination should have different mechanisms of action

Most FDCs have the following demerits:

• Differing pharmacokinetics of constituent drugs has the problem of frequency of administration of the combination

• Dosage alteration of one API is not possible without alteration of the other API

• There are increased chances of drug interactions and adverse drug events compared with both drugs given individually.

Strategy for marketing

The pharmaceutical companies dodge the buyers by using catch lines like "ibuprofen for pain and paracetamol for fever or paracetamol for central action and ibuprofen for peripheral action ".

There's is no synergistic action when two drugs combined act on same enzyme. So such irrational FDCs which are prepared by combining two NSAIDs in no way enhance the efficacy of the treatment and only add the cost of therapy and adverse effects.

Thus approval and acceptance of such irrational medicine hangs like an albatrossaround the neck of medical fraternity.

Combination of NSAIDs with antispasmodic agents likedicyclominemarketed in India were not only irrational but also were hazardous.

Anticholinergic antispasmodic drug inhibits sweating. On the other hand, antipyretic drugs promote sweating and help in heat dissipation.

Hence combination of these drugs can result in dangerous elevation of temperature. Thus the above FDC was banned in India.

FDCs definitely have a clear advantage over single drug preparations.

It is easier for a patient to take single tablet than multiple pills. Hence they improve patient compliance. FDCs like Zimnic AZ have flourished in Indian market.

Many such FDCs are used worldwide to treat difficult cases like in case of HIV, TB and Malaria.

70% of NSAID combinations, which were used as pain relievers were being marketed in India without approval by central government, according to a study published in Journal of Public library of science (PLOS) in May, following which the unapproved drugs were banned immediately

Industry Prospective

People in pharmaceutical industry say that the combination drugs are "money-spinning" as they are prescribed rampantly by the doctors. They also put a clever remark as a single pill can cover multiple possible symptoms, said a physician employed by a pharmaceutical company.

Between 2011 and 2014, India's fixed-dose combination market grew more than 40% in Rupee terms, according to IMS Health.

FIXED DOSE COMBINATIONS THAT CHANGE THE TREATMENT COMPLIANCE OF VARIOUS DISEASES

Fixed Dose Combinations That Change The Treatment Compliance Of Tuberculosis

Tuberculosis

Tuberculosis patient needs to take multiple drug therapy for at least 6 months, which understandably leads to patient non - compliance and there are high chances that the patient quit the therapy before completion which leads to failure of the therapy and ultimately leads to emergence of drug resistance. Hence T.B remains one of the most important communicable diseases with high mortality and morbidity rates.

Thus anti tubercular therapy given in the form of FDCs would be a clever remark to the problem as it reduces the number of tablets to be consumed by patients, and hence lead to increase patient compliance which shows less failure rates which ultimately makes no room for emergence of drug resistance.

The rationale for using FDCs for TB is that TB requires multi-drug therapy.[24]

The development of FDCs in treatment of TB was facilitated by the fact that the API were generic and their efficacy and safety had already been proven.

Anti-TB FDC formulations consists two or more first-line anti-TB drugs (namely rifampicin, isoniazid, pyrazinamide and ethambutol) in a fixed dose in a single dosage form.

The advantages of use of these DOTS FDCs are:

• Efficacy and Safety;

• Dosage adjustment according to individual need;

• Better management of DOTS

• Simplified treatment;

• Simplified drug, shipping, supply management and distribution;

• Reduction in risk of emergence of drug-resistant strains.

WHO and IUATLD has recommend the use of Anti-TB FDC formulations as routine practice in the treatment of TB and FDCs are also included in the WHO Model List of Essential Drugs.[25][26][27][28]

WHO-recommended strengths of FDCs of first-line anti-TB drugs[29][30]

Doses in mg/kg bodyweight

		Rifampicin (R)	Isoniazid (H)	Pyrazinamide (Z)	Ethambutol (E)	Thioacetazone (T)	Streptomycin (S)
Mode of action		Bactericidal	Bactericidal	Bactericidal	Bacteriostatic	Bacteriostatic	Bactericidal
Daily use	Single formulations	10(8-12)*	5(4-6)*	25(20-30)*	15(15-20)*	2.5*	15(12-18)*
	FDCs (Tablets)						
	R+H+Z+E	150	75	400	275	-	-
	R+H+Z	150	75	400	-	-	-
	R+H+Z (Paediatric)	60	30	150	-	-	-
	R+H	150	150	-	-	-	-
	R+H	150	75	-	-	-	-
	R+H (Paediatric)	60	30	-	-	-	-
	H+E	-	150	-	400	-	-
	H+T	-	100	-	-	50	-
	H+T	-	300	-	-	150	-
Inter-mittent use (3 times weekly)	Single formulations	10(8-12)*	10(8-12)*	35(30-40)*	30(25-35)*	Not applicable	15(12-18)*
	FDCs (Tablets)						
	R+H+Z	150	150	500	-	-	-
	R+H	150	150	-	-	-	-
	R+H (Paediatric)	60	60	-	-	-	-

WHO recommended strengths and dose schedule of FDCs

Patient body weight (kg)	Intensive Phase		Continuation Phase	
Children	2 months		4 months	
	RHZ (no. of tablets daily)		RH (no. of tablets daily)	RH (no. of tablets thrice weekly)
≤7	1		1	1
8-9	1.5		1.5	1.5
10-14	2		2	2
15-19	3		3	3
20-24	4**		4	4
25-29	5**		5	5
Adults	2 months		4 months	6 months
	RHZE (daily)	RHZ (daily)	RH (daily and thrice weekly)	HE (daily)
30-39	2	2	2	1.5
40-54	3	3	3	2
55-70	4	4	4	3
≥ 70	5	5	5	3

Better management of DOTS using FDCs

After the diagnosis of TB, FDCs have been made available with the required drugs in correct proportions in a single dosage form.

Meanwhile it has also reduced the burden that the health care professionals had to shoulder in terms of monitoring the DOTS strategy.

Thus, it reflects that the FDCs have untangled the complexities in the procedures involved in DOTS strategy to a great extent and aided in its effective implementation. [26]

Simplifying drug supply management

The FDCs infrequently confront the "out of stock" circumstance not at all like the individual formulation wherein there is lack of buffer stock, delay in receiving an order and expiration of stock without substitutions being accessible.

The FDCs have a less formulation to consider, henceforth its simpler to count the drugs needs, advantageous to request, send and disperse and therefore there is less strain on staff in national TB program.

In addition theutilization of FDC tablets limit the abuse of rifampicin for conditions other than TB[29]

Reduced risk of emergence of drug-resistant strains

If we get down to the nitty-gritty of TB treatment in India, we find that the patients have settled for monotherapy despite the prescribed multi drug therapy because of the practical problems like temporary lack of stock of one or more drugs, errors in dispensing or because of the psyche of patients that, the more the number of drugs, the more the adverse effects or the reluctance to spend their life savings on treatment. [31]

Fixed Dose Combinations That Change The Treatment Compliance Of HIV

Highly active antiretroviral therapy (HAART) has transferred dramatically the mortality and morbidity picture of the HIV infection in the inflated world[32].

Over the last few years, increased survival rate of HIV-infected patients has been credited to the widespread use of HAART, and has been reported to improve the condition even in a developing country [33]

Fixed-dose combinations (FDCs)

The developments of FDCs have reduced the cost of ARV drugs dramatically and have improved the access todrugs.

They are now being available as once daily combo packs. Hence guidelines from WHO and other international bodies have recommended the use of FDCs as a step to facilitate optimal treatment of HIV, after they were been regarded as standard, simpler and potentially more reliable way of treating HIV.

Also the extension of FDCs to use in HIV is crucial as the therapy here is lifelong and more demanding.

Advancements of FDC details basically focus on guaranteeing the physical and chemical compatibility of API in FDC.

Moreover, the in-vitro disintegration profile of individual medications and FDC should be same as patented drug.

Drug compatibility studies have demonstrated physical in compatibility for 3TC with d4T, and NVP (Nevirapine) with d4T. Notwithstanding, 3TC and NVP were perfect.

Subsequently the plan of d4T/3TC/NVP is a bilayer tablet, where d4T is one layer and 3TC and NVP another layer and in this manner the physical contradiction has been limited.

The studies carried out on chosen excipient for formulating FDCs did not reveal any sort of interaction which indicated the better compatibility of the combination

A similar approach has been utilized for assembling a FDC of AZT/3TC/NVP However; in this case compatibility was seen between all of the individual drugs. Hence all medications were combined into a single pill.

FDC formulations available in India for treatment of HIV

Formulation	Form and strength (mg)	Manufacturers	Dose
zidovudine/lamivudine/nevirapine	tablet 300/150/200	Cipla Genix (Hetero) Immunus– Aurbindo	1 tab orally twice daily
stavudine/lamivudine/nevirapine (30) stavudine/lamivudine/nevirapine (40)	tablet 30/150/200 tablet 40/150/200	Cipla Immunus– Aurbindo Ranbaxy	1 tab orally twice daily (wt< 60 kg) 1 tab orally twice daily (wt>60 kg)
zidovudine/lamivudine	tablet 300/150	Cipla Genix (Hetero) Immunus– Aurbindo Ranbaxy	1 tab orally twice daily
stavudine/lamivudine (30) stavudine/lamivudine (40)	tablet 30/150 tablet 40/150	Cipla Genix (Hetero) Immunus– Aurbindo Ranbaxy	1 tab orally twice daily (wt<60 kg) 1 tab orally twice daily (wt>60 kg)

Safety, efficacy and quality of FDCs

There are constrained information on the efficacy and safety of FDC s in treatment of HIV infection.

In spite of the fact that there have been problematic reports of lack of active ingredients in some generic FDCs, [34] in one investigation of NVP in generic FDCs, API in both individual tablets and in FDC was observed to be satisfactory [35]

NVP based HAART FDC formulations showed safety and good clinical and immunological benefit among the ARV- naive- HIV infected patients in India.

The patients have found it more easier to cling on as the regimen were convenient and well tolerated.

It also helped in reserving future treatment options in patients with drug failure. Therefore first line regimen in programmes ARV therapy consist NVP based HAART in resource limited settings.

Fixed Dose Combinations That Change TheTreatment Compliance Of Malaria

There are no less than 300 million intense instances of malaria every year globally, bringing about more than a million deaths.

Nearly 90% of all death happens in Africa, mainly in youthful kids. Malaria is Africa's driving reason for under-five mortality (20%) and constitutes 10% over all disease burden of the continent. It accounts for 30-50% of inpatient admissions, 40% of public health expenditure and 50% of outpatient visits who carry the risk of transmission

Resistance of P. falciparum to chloroquine showed up at the same time in Colombia in 1960 and on the frontier between Cambodia and Thailand.

In Asia, chloroquine- resistance was bound to Indochina until the point that the 1970s, when it reached out toward the west and towards the neighbouring islands toward the south and east.

Today, just couple of nations in Central America north of the Panama Canal, including Haiti and Dominican Republic, don't report chloroquineresistant falciparum malaria.

Amodiaquine stays valuable in territories where there is a less resistance to chloroquine, disregarding the consequences of a few studies that suggest its low efficacy, maybe on the grounds that inadequate doses were included[(36)]

On the grounds of developing resistance to chloroquine, the sulfadoxine-pyrimethamine(s/p) FDC was used to replace chloroquine.

South Africa was the first country to take this initiative and later Malawi took the lead and changed its policy to S/P as the first line drug.

Other African countries went after the same example. But ,because of the massive use of this product, the combination became almost totally ineffective at the beginning of 1980s in many parts of East Africa, Thailand and neighbouring countries.

In April 2001, WHO made a systematic review of existing data on combination therapy for malaria to undertake and to identify appropriate combinations for use, particularly in African countries.

The technical consultation took the form of presentations based on working papers and plenary discussions, on the basis of which specific conclusions and recommendations were agreed.

The proceedings of the meeting and working papers formed the basis of a WHO report. (37)

It also recommended the fixed dose combination of following:-

1. Artemether/Lumenfantrine

2. Artesunate plus Amodiaquine

3.Artesunateplus Sulfadoxine/Pyrimethamine, in areas

where Sulfadoxine/Pyrimethamineefficacy is high;

4. Amodiaquineplus Sulfadoxine/Pyrimethamine, in areas where efficacy of both drugs is high.

Introduction of the FDCs in treatment of malaria immediately showed the better outcome in Latin America and African countries particularity in uncomplicated plasmodium falciparum

The Roll back malaria (RBM) is committed to promote FDC anti malarial products particularly ACTs especially in the areas of resistance.

However the RBM is struggling hard to help cross the hurdles faced by the manufacturers in the production of such products, instigating the National malaria control programmes to adopt the new FDCs and ensuring promising qualities of the products to regulators!

MATERIAL AND METHODS

MATERIAL AND METHODS

STUDY DESIGN : Prospective open label study.

LOCUS OF STUDY

SAMPLE SIZE: With 95%confidence level, anticipated prevalence of the FDC as 84% and desired precision at±2% the minimum Sample size is 1291≤1300[17].

Formula used,$n = \frac{z^2 p(1-p)}{d^2}$

Where n=sample size.

z=stastistic for a level of confidence.

p=expected prevalence.

d=precision.

A total of 1300 prescriptions from the patients attending OPD of Shri B M Patil Medical College Hospital were collected at the pharmacy &were included in the study(the identity of the patient was not disclosed).

The prescriptions containing FDCs were analyzed using the tool designed on the basis of WHO guidelines for registration of fixed dose combination medicinal product[38,39]

Tool to assess the rationality of fixed dose combinations

1. Active pharmacological ingredient along with strength .....
   .....
   .....

2. API

	API		
1	Approved by DCGI	Yes (+1)	No (−1)
2	Ingredient: Banned or Controversial	Yes (−1)	No (+1)

API = Active pharmacological ingredient, DCGI = Drug controller general of India

3. Listing in EML WHO/National/Both/None
   (+1) (0)
4. Efficacy (text book/reference book/pub med/medline/ other)

1	API	Yes (+1)	No (0)
2	FDC	Yes (+1)	No (0)

API = Active pharmacological ingredient, FDC = Fixed dose combination

5. Safety (text book/reference book/pub med/medline/other)

1	API	Yes (+1)	No (0)
2	FDC	Yes (+1)	No (0)

API = Active pharmacological ingredient, FDC = Fixed dose combination

6. Pharmacokinetic (absorption/distribution/metabolism/ excretion/BA/BE/t ½)
   - Interaction Favourable/Unfavourable/Not affected
     (+1) (−1) (0)
7. Pharmacodynamic-M/A of each ingredient
   Similar (0)/Different (+1)
8. Advantage of FDC
   - Reduced Yes (+1) No (0)
   - Less ADR Yes (+1) No (0)
   - Convenient Yes (+1) No(0)
     (frequency or pill count)

   Total score: 12

   Score ≥7: Rational FDC Score ≤6: Irrational FDC

Based on the tool FDCs have been grouped under following categories.

1. Rational as per WHO.

2. Rational included in two most recent Indian essential drug lists.

3. Rational which were pharmacologically correct in combinations but not included in WHO or Indian essential drugs lists.

4. Irrational

5. Absurd.

STATISTICAL ANALYSIS:

- All the quantitative variables have been expressed as mean and standard deviation and qualitative variables are expressed as percentages and proportions

RESULTS

RESULTS

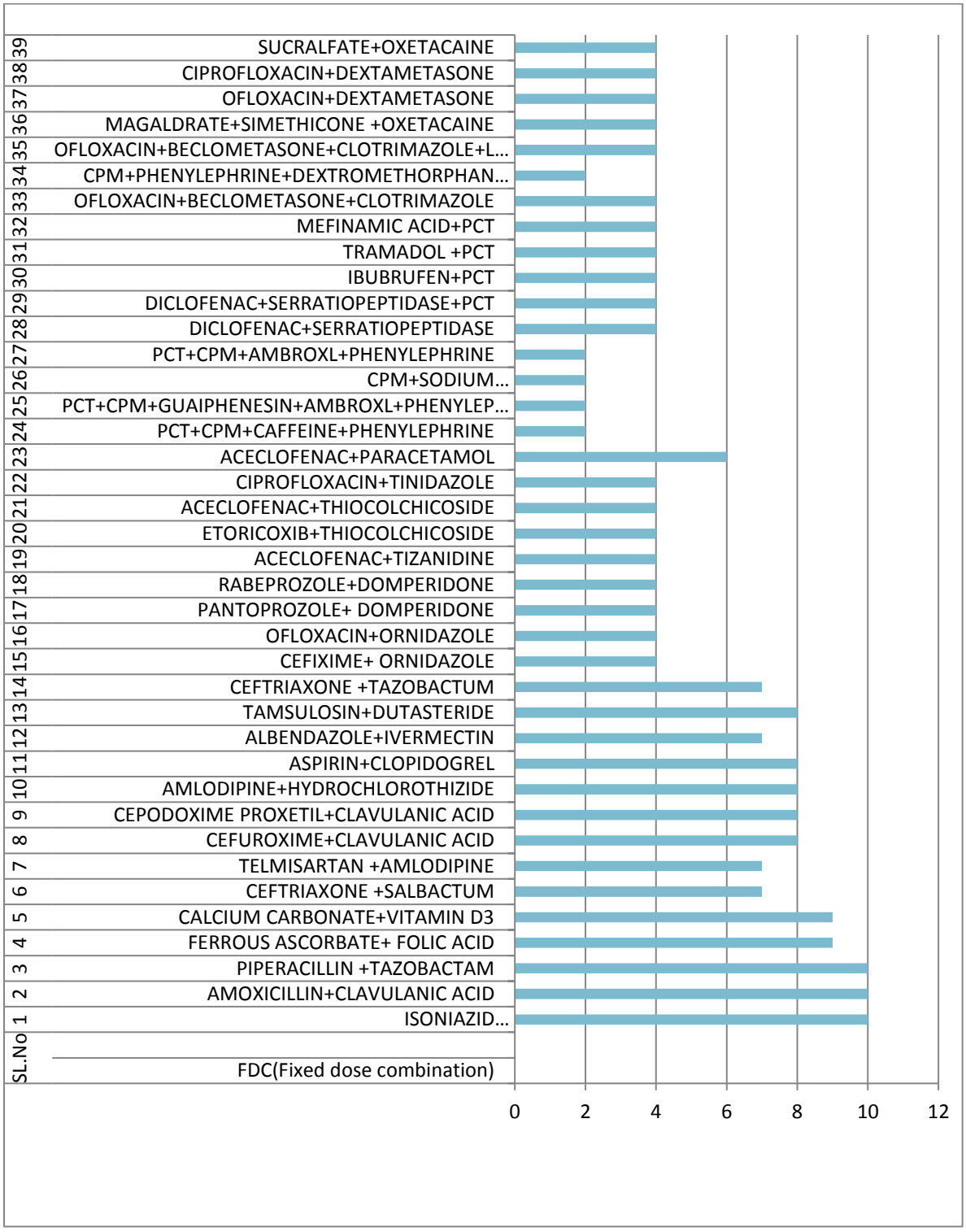
A total of 1300 prescriptions were collected for the study

And a total of 39 fixed dose combinations were found prescribed and were analysed as per the tool

Sl.no	Fixed Dose Combinations
1.	ISONIAZID +RIFAMPACIN+PYRIZINAMIDE+ETHAMBUTOL
2.	AMOXICILLIN+CLAVULANIC ACID
3.	PIPERACILLIN +TAZOBACTAM
4.	FERROUS ASCORBATE+ FOLIC ACID
5.	CALCIUM CARBONATE+VITAMIN D3
6.	CEFTRIAXONE +SALBACTUM
7.	TELMISARTAN +AMLODIPINE
8.	CEFUROXIME+CLAVULANIC ACID
9.	CEPODOXIME PROXETIL+CLAVULANIC ACID
10	AMLODIPINE+HYDROCHLOROTHIZIDE
11	ASPIRIN+CLOPIDOGREL
12	ALBENDAZOLE+IVERMECTIN
13	TAMSULOSIN+DUTASTERIDE
14	CEFTRIAXONE +TAZOBACTUM
15	CEFIXIME+ ORNIDAZOLE
16	OFLOXACIN+ORNIDAZOLE
17	PANTOPROZOLE+ DOMPERIDONE

18	RABEPROZOLE+DOMPERIDONE
19	ACECLOFENAC+TIZANIDINE
20	ETORICOXIB+THIOCOLCHICOSIDE
21	ACECLOFENAC+THIOCOLCHICOSIDE
22	CIPROFLOXACIN+TINIDAZOLE
23	ACECLOFENAC+PARACETAMOL
24	PCT+CPM+CAFFEINE+PHENYLEPHRINE
25	PCT+CPM+GUAIPHENESIN+AMBROXL+PHENYLEPHRINE
26	CPM+SODIUM CITRATE+PHENYLEPHRINE+MENTHOL
27	PCT+CPM+AMBROXL+PHENYLEPHRINE
28	DICLOFENAC+SERRATIOPEPTIDASE
29	DICLOFENAC+SERRATIOPEPTIDASE+PCT
30	IBUBRUFEN+PCT
31	TRAMADOL +PCT
32	MEFINAMIC ACID+PCT
33	OFLOXACIN+BECLOMETASONE+CLOTRIMAZOLE
34	CPM+PHENYLEPHRINE+DEXTROMETHORPHAN HYDROBROMIDE
35	OFLOXACIN+BECLOMETASONE+CLOTRIMAZOLE+LIDOCAIN
36	MAGALDRATE+SIMETHICONE +OXETACAINE
37	OFLOXACIN+DEXTAMETASONE
38	CIPROFLOXACIN+DEXTAMETASONE
39	SUCRALFATE+OXETACAINE

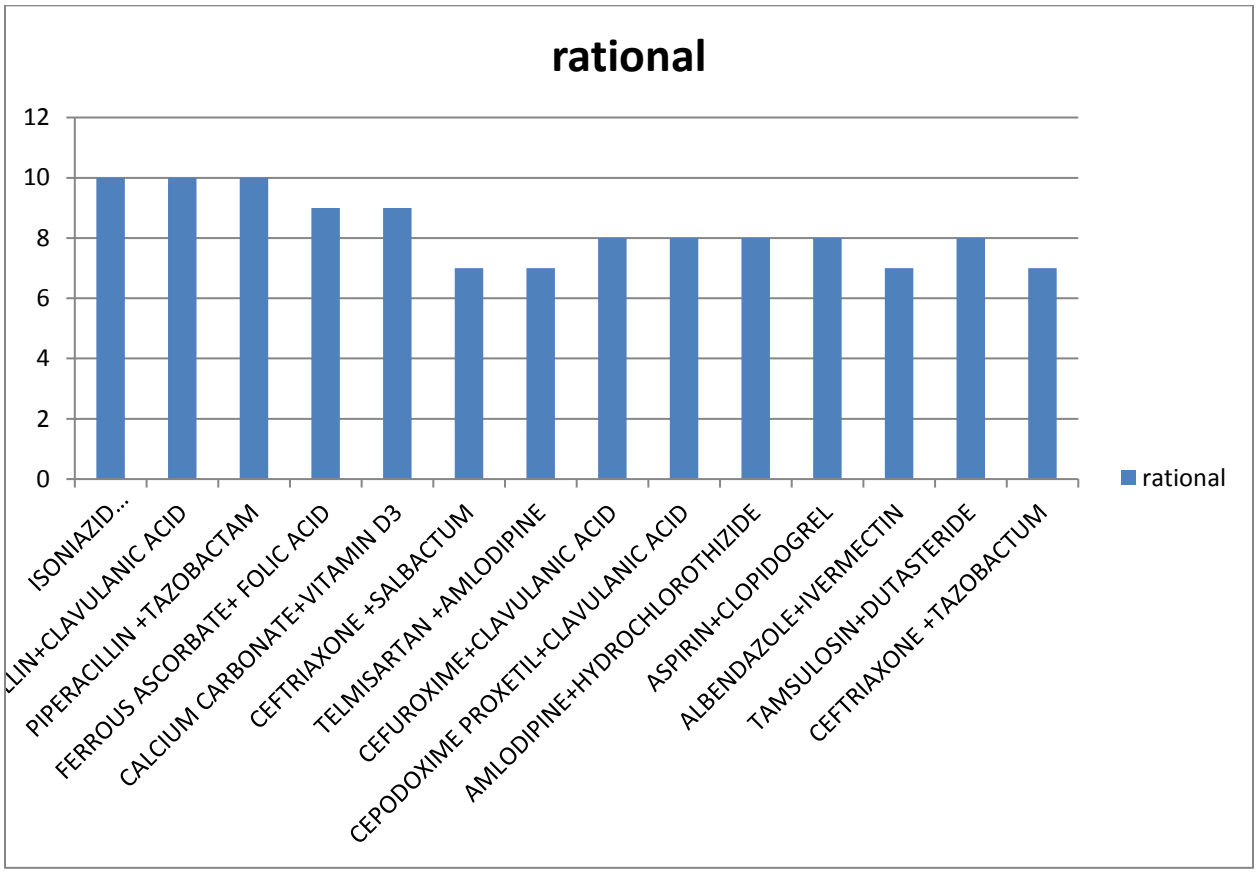
Graph of total 39 FDCs and there score



Rational FDC s

FIXED DOSE COMBINATIONS	SCORE
ISONIAZID +RIFAMPACIN+PYRIZINAMIDE+ETHAMBUTOL	10
AMOXICILLIN+CLAVULANIC ACID	10
PIPERACILLIN +TAZOBACTAM	10
FERROUS ASCORBATE+ FOLIC ACID	9
CALCIUM CARBONATE+VITAMIN D3	9
CEFTRIAXONE +SALBACTUM	7
TELMISARTAN +AMLODIPINE	7
CEFUROXIME+CLAVULANIC ACID	8
CEPODOXIME PROXETIL+CLAVULANIC ACID	8
AMLODIPINE+HYDROCHLOROTHIZIDE	8
ASPIRIN+CLOPIDOGREL	8
ALBENDAZOLE+IVERMECTIN	7
TAMSULOSIN+DUTASTERIDE	8
CEFTRIAXONE +TAZOBACTUM	7

Mean score of rational FDCs was 8 ± 0.28 maximum was 10 minimum was 7

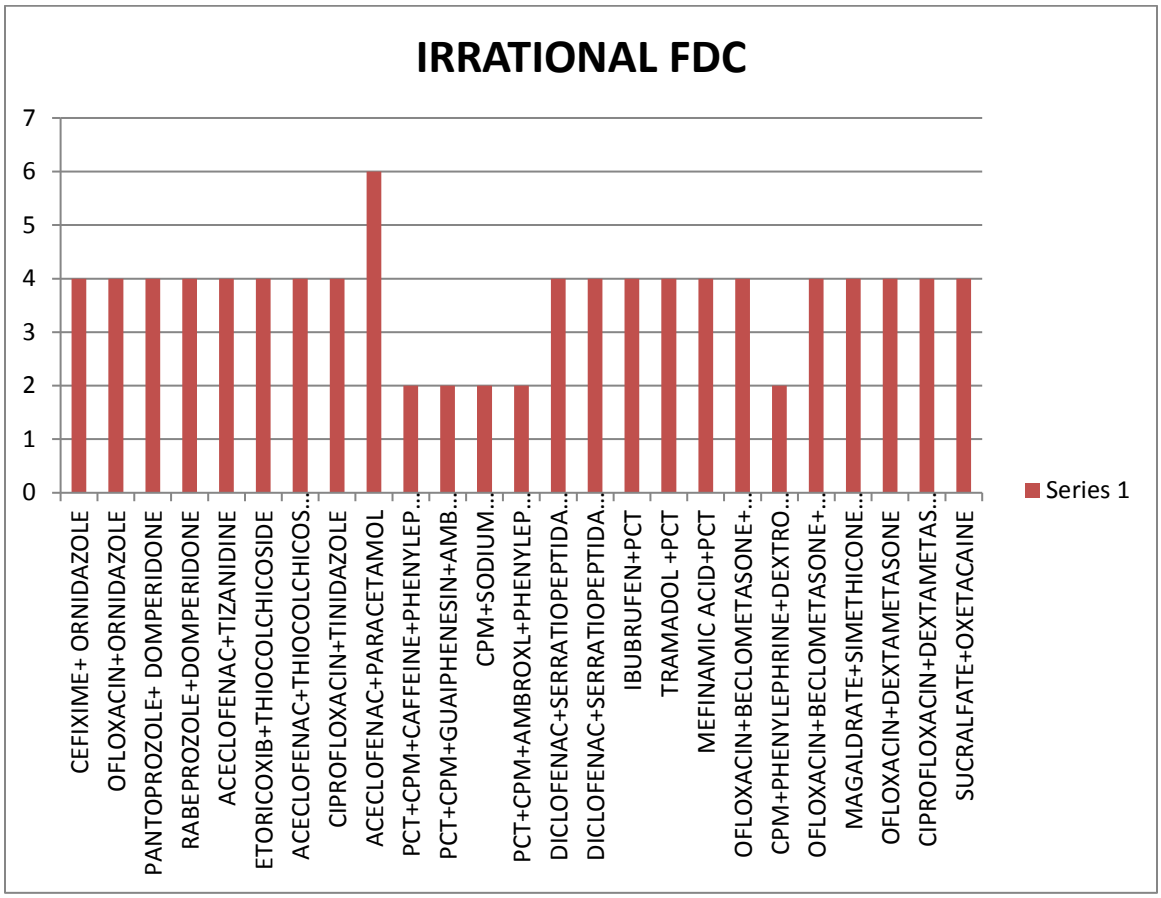

rational
12
10
8
6
4
2
0
ISONIAZID...
LLIN+CLAVULANIC ACID
PIPERACILLIN +TAZOBACTAM
FERROUS ASCORBATE+ FOLIC ACID
CALCIUM CARBONATE+VITAMIN D3
CEFTRIAXONE +SALBACTUM
TELMISARTAN +AMLODIPINE
CEFUROXIME+CLAVULANIC ACID
CEPODOXIME PROXETIL+CLAVULANIC ACID
AMLODIPINE+HYDROCHLOROTHIZIDE
ASPIRIN+CLOPIDOGREL
ALBENDAZOLE+IVERMECTIN
TAMSULOSIN+DUTASTERIDE
CEFTRIAXONE +TAZOBACTUM
rational

Total number of Irrational FDC s

FIXED DOSE COMBINATIONS	SCORE
CEFIXIME+ ORNIDAZOLE	4
OFLOXACIN+ORNIDAZOLE	4
PANTOPROZOLE+ DOMPERIDONE	4
RABEPROZOLE+DOMPERIDONE	4
ACECLOFENAC+TIZANIDINE	4
ETORICOXIB+THIOCOLCHICOSIDE	4
ACECLOFENAC+THIOCOLCHICOSIDE	4
CIPROFLOXACIN+TINIDAZOLE	4
ACECLOFENAC+PARACETAMOL	6
PCT+CPM+CAFFEINE+PHENYLEPHRINE	2
PCT+CPM+GUAIPHENESIN+AMBROXL+PHENYLEPHRINE	2
CPM+SODIUM CITRATE+PHENYLEPHRINE+MENTHOL	2
PCT+CPM+AMBROXL+PHENYLEPHRINE	2
DICLOFENAC+SERRATIOPEPTIDASE	4
DICLOFENAC+SERRATIOPEPTIDASE+PCT	4
IBUBRUFEN+PCT	4
TRAMADOL +PCT	4
MEFINAMIC ACID+PCT	4
OFLOXACIN+BECLOMETASONE+CLOTRIMAZOLE	4
CPM+PHENYLEPHRINE+DEXTROMETHORPHAN	2

HYDROBROMIDE	
OFLOXACIN+BECLOMETASONE+CLOTRIMAZOLE+LIDOCAINE	4
MAGALDRATE+SIMETHICONE +OXETACAINE	4
OFLOXACIN+DEXTAMETASONE	4
CIPROFLOXACIN+DEXTAMETASONE	4
SUCRALFATE+OXETACAINE	4

Mean score of irrational FDCs was 3 ± 0.68 maximum was 6 minimum was 2


IRRATIONAL FDC
7
6
5
4
3
2
1
0
CEFIXIME+ ORNIDAZOLE
OFLOXACIN+ORNIDAZOLE
PANTOPROZOLE+ DOMPERIDONE
RABEPROZOLE+DOMPERIDONE
ACECLOFENAC+TIZANIDINE
ETORICOXIB+THIOCOLCHICOSIDE
ACECLOFENAC+THIOCOLCHICOS...
CIPROFLOXACIN+TINIDAZOLE
ACECLOFENAC+PARACETAMOL
PCT+CPM+CAFFEINE+PHENYLEP...
PCT+CPM+GUAIPHENESIN+AMB...
CPM+SODIUM...
PCT+CPM+AMBROXL+PHENYLEP...
DICLOFENAC+SERRATIOPEPTIDA...
DICLOFENAC+SERRATIOPEPTIDA...
IBUBRUFEN+PCT
TRAMADOL +PCT
MEFINAMIC ACID+PCT
OFLOXACIN+BECLOMETASONE+...
CPM+PHENYLEPHRINE+DEXTRO...
OFLOXACIN+BECLOMETASONE+...
MAGALDRATE+SIMETHICONE...
OFLOXACIN+DEXTAMETASONE
CIPROFLOXACIN+DEXTAMETAS...
SUCRALFATE+OXETACAINE
Series 1

RATIONAL AS PER WHO ESSENTIAL DRUG LISTS

ISONIAZID +RIFAMPACIN+PYRIZINAMIDE+ETHAMBUTOL	10
AMOXICILLIN+CLAVULANIC ACID	10
FERROUS ASCORBATE+ FOLIC ACID	9

RATIONAL INCLUDED IN TWO MOST RECENT INDIAN ESSENTIAL DRUG LISTS.

ISONIAZID +RIFAMPACIN+PYRIZINAMIDE+ETHAMBUTOL	10
AMOXICILLIN+CLAVULANIC ACID	10
FERROUS ASCORBATE+ FOLIC ACID	9
PIPERACILLIN +TAZOBACTAM	10

RATIONAL WHICH ARE PHARMACOLOGICALLY CORRECT IN COMBINATIONS BUT NOT INCLUDED IN WHO OR INDIAN ESSENTIAL DRUGS LISTS

CALCIUM CARBONATE+VITAMIN D3	9
CEFTRIAXONE +SALBACTUM	7
TELMISARTAN +AMLODIPINE	7
CEFUROXIME+CLAVULANIC ACID	8
CEPODOXIME PROXETIL+CLAVULANIC ACID	8
AMLODIPINE+HYDROCHLOROTHIZIDE	8
ASPIRIN+CLOPIDOGREL	8
ALBENDAZOLE+IVERMECTIN	7
TAMSULOSIN+DUTASTERIDE	8
CEFTRIAXONE +TAZOBACTUM	7

IRRATIONAL. FDC

CEFIXIME+ ORNIDAZOLE	4
OFLOXACIN+ORNIDAZOLE	4
PANTOPROZOLE+ DOMPERIDONE	4
RABEPROZOLE+DOMPERIDONE	4
ACECLOFENAC+TIZANIDINE	4
ETORICOXIB+THIOCOLCHICOSIDE	4
ACECLOFENAC+THIOCOLCHICOSIDE	4
CIPROFLOXACIN+TINIDAZOLE	4
ACECLOFENAC+PARACETAMOL	6
DICLOFENAC+SERRATIOPEPTIDASE	4
DICLOFENAC+SERRATIOPEPTIDASE+PCT	4
IBUBRUFEN+PCT	4
TRAMADOL +PCT	4
MEFINAMIC ACID+PCT	4
OFLOXACIN+BECLOMETASONE+CLOTRIMAZOLE	4
OFLOXACIN+BECLOMETASONE+CLOTRIMAZOLE+LIDOCAINE	4
MAGALDRATE+SIMETHICONE +OXETACAINE	4
OFLOXACIN+DEXTAMETASONE	4
CIPROFLOXACIN+DEXTAMETASONE	4
SUCRALFATE+OXETACAINE	4

ABSURD.

CPM+PHENYLEPHRINE+DEXTROMETHORPHAN HYDROBROMIDE	2
PCT+CPM+CAFFEINE+PHENYLEPHRINE	2
PCT+CPM+GUAIPHENESIN+AMBROXL+PHENYLEPHRINE	2
CPM+SODIUM CITRATE+PHENYLEPHRINE+MENTHOL	2
PCT+CPM+AMBROXL+PHENYLEPHRINE	2

DISCUSSION

DISCUSSION

Rational use of medicines in therapeutics is a much bigger felt need than ever before.

Rational use of medicine means use of a right medicine, in the right manner, at right time, in the right type of patients, at a right cost i.e. "the rule of right"[40].

Among many reasons of irrational use of medicines, one is the use of unnecessary Fixed-dose Drug Combinations (FDCs). The aim of the present study was to find out the irrational of FDCs in tertiary care hospital.

The following study was done to access the rationality of the FDCs. The studies have shown relation between the FDCs and pattern of prescription in various places and diseases.

Total of 39 FDCs were analysed for their rationality. Of them, 36% (14) were rational, 64% (25) were found to be Irrational, 8 %(3) rational as per WHO and 10% (4) rational according to Indian essential drug list. Most of the combinations were in the oral form, 85% were topical preparation and the rest 5% were to be administered parenterally. Similar studies were undertaken by Singh etal., Of the analysed 225 drugs, only 20% (45) met the recommendations of WHO list [41].

Also according to Dahiya act etal., only 20% of the prescriptions fitted into the criteria present in WHO EML 2011.[42]

As per the BalateTal., 92.7% prepartions were to be given per orally , 5.9% topically and 1.4% parenteral route[43]

The present study revealed that 64% (25) FDCs have the potential to cause adverse drug reactions because of their active pharmacological ingredients'.

Singh et al., also showed in his study out of 270 combinations, 150 (56.81%) FDCs were adding risk of adverse drug reactions. More than 50% of combinations showed adverse drug reactions in studies by Rayasam et al., and McGettigan et al.,[44][45]

Example: The FDC containing paracetamol and NSAID.

Although approved by CDSCO, the above FDC is irrational.

The components of the FDC do not complement each other's action and hence there is no synergistic effect.

NSAIDs possess both anti- pyretic and analgesic property more than paracetamol. In addition the two drugs when combined have increased chances of causing liver toxicity. Thus above FDC fails to be rational.[46]

In spite of withdrawing Thiocolchicoside by FDA from American and European market for it causation of anueploidy, there are still11 combinations in CDSCO list with the same component which are marketed in India.[45]

On the other hand, The FDCs of Anti – infective drugs and Anti-retroviral therapy have been credited for their rational preparations. [47]

Anti cough and cold remedies

PCT+CPM+CAFFEINE+PHENYLEPHRINE

PCT+CPM+AMBROXL+PHENYLEPHRINE

CPM+SODIUM CITRATE+PHENYLEPHRINE+MENTHOL

PCT+CPM+GUAIPHENESIN+AMBROXL+PHENYLEPHRINE

Anti cough and cold remedies

For a formulation to be rational as a cough remedy;it shouldsatisfythefollowingspecifications:

1. Twoexpectorantsshouldnotbeaddedinasingleformulation.
2. Abronchodilatorshouldbethemainconstituent in formulations prescribed for asthmaorchronicbronchitis.
3. Sputum expectorant facilitator likepotassium iodidemaybeaddediftheformulationneedsit.
4. Above all a formulation should have onlyone potentactivePharmaceuticalingredientwhichisevidencebasedinprovidingdesiredrelief.

Bromhexinehydrochloride4mg,Phenylephrinehydrochloride2.5mg,ChlorpheniramineMaleate2mgandParacetamol125mg.

Thisisanirrationalcombinationasbromhexineisamucolyticandchlorpheniramineisanantihistaminicwithanticholinergicproperties.Amucolyticwhichincreasesthemucussecretionsshouldnotbegivenincombination withchlorpheniraminewhichdries upthesecretions .thus CPM interferes mucolytic action of bromhexine.[48]

Ascoughandcoldarenotalwaysaccompaniedbyfever,additionofparacetamolexpos estheconsumertothe undesired effectofthe antipyretic unnecessarily.Itiswellknownthat"H1antagonistsarewithoutvalueincombatingthe commoncold.Theweakanticholinergiceffectsoftheolderagentsmaytendtolessenrhinorrhea butthiseffectmaydomoreharmthangoodbecause of its tendencytoinducesomnolence." [49]

NSIDS with PCT

DICLOFENAC+SERRATIOPEPTIDASE

DICLOFENAC+SERRATIOPEPTIDASE+PCT

IBUBRUFEN+PCT

TRAMADOL +PCT

MEFINAMIC ACID+PCT

ACECLOFENAC+PARACETAMOL

ACECLOFENAC+TIZANIDINE

ETORICOXIB+THIOCOLCHICOSIDE

ACECLOFENAC+THIOCOLCHICOSIDE

As already mentioned, combining paracetamol with another NSAIDs has no advantage and only leads to nephrotoxicity.[50]

Similarly as the NSAIDs have no action against the colicky pain, addition of the same with anti-spasmodics again has no advantage.[51][52]

Adding Paracetamolto another NSAID (Diclofenac, Aceclofenac, and Ibuprofen) does not offer additional benefit, but increases the chances of nephrotoxicity. [50]

Combining NSAIDs with antispasmodics (Dicyclomine, Drotaverine) is irrational as the former has no role in colicky pain which only the latter relieve. [51][52]

By amplifying the risk of GI side effects, the skeletal muscle relaxants provide no additional benefit.

Serratiopeptidase has not undergone any controlled clinical trials yet claims to have proteolytic enzyme activity which relieve inflammation.

Thus the preparation containing this product provide no Anti Inflammatory effects but onlyoffers cost burden[53]

PPI+ DOMPERIDONE

It is claimed to facilitate absorption of PPI by increasing gastric motility, however the combination has not been shown to be superior then Omeprazole or Pantaprozoleused alone in treatment of peptic ulcer's or any other conditions such as reflex oesophagitisor dyspepsia.

Domperidone is short acting requiring three times a day administrationwhile PPI is long acting used once a day resulting in pharmacokinetic mismatch.[54]

FluoroquinoloneswithNitroimidazoles

Cephalosporins with Nitroimidazoles

CIPROFLOXACIN+TINIDAZOLE

OFLOXACIN+ORNIDAZOLE

CEFIXIME+ ORNIDAZOLE

The combination of Fluoroquinolones andNitroimidazoles are used extensively for various types of diarrhoea and dysentery

Ciprofloxacin, Ofloxacin ,Cefiximeare indicated in bacterial infection and Tinidazole ,Ornidazoleare indicated in amoebic infection

Both are useful together if there is a mixed infection which is very uncommon ~ 5-10%

The Doctors have to note that the Nitoimidazoles are of no value in treating bacterial dysentery and Fluroqinoloes are not at all necessary in treatment of amoebic dysentery. They only increase the cost and adverse effects

The frequency of the administration of Fluoroquinolones and Nitroimidazolesare different

Fluoroquinolones like Ciprofloxacin, Ofloxacin are to be administered twice daily While Nitroimidazoles like Tinidazole is to be administered once daily, Metronidazole is administered three times a daily [55]

Thus such FDCs are irrational.

Fluoroquinolones with Steroid

CIPROFLOXACIN+DEXAMETHASONE

OFLOXACIN+DEXAMETHASONE(ear drop)

A study conducted by A. Panchasara1 showed that addition of steroid does not have any sort of added advantage in treatment of CSOM.

In fact the study came out to recommend not use combination as clinical symptom relief was good with Ofloxacin alone [56]

Fluoroquinolone with Steroid, Antifungal agent, Local Anaesthetic

Ofloxacin+Beclometasone+Clotrimazole+Lidocaine

Ofloxacin+Beclometasone+Clotrimazole

Ofloxacin an Fluoroquinolone has an anti bacterial action were as Clotrimazoleis a fungistatic drug , It is very less often that a disease is combined with both fungial as well as bacterial infection

A study conducted by Wannanukul S et.al conducted a comparative study on efficacy of antifungal drug used alone and along with Steroid combination

It revealed that there was nostatistically significant difference seen in the outcome of the disease [57]

SUMMARY

SUMMARY

Fixed dose combinations (FDCs) is a product containing two or more active drugs used in a single dosage form for a particular indication. Prescribing a FDC is a routine in clinical practice. Use of FDC has been associated with many advantages as well as disadvantages limiting its use so the study was intended to check the rationality of FDCs prescribed in a tertiary care hospital vijayapura .Out of 1300 prescriptions collected for the study , 39 fixed dose combinations were found prescribed and were analysed as per the tool. Results ,Out of total 39 FDCs analysed for rationality, 36% (14) have found to be rational, 64 %(25) were irrational , 8%(3) rational as per WHO, 10%(4)rational as per Indian essential drug list ,28% (10)pharmacologically correct FDCs.Maximum combinations were in oral dosage form 85% followed topical 15%and rest in parenteral dosage form 5%.

That included following combinations Anti cough and cold remedies, NSIDS with, Fluoroquinolones+dexamethasone, Fluoroquinolones+Steroid+Antifungal+LocalAnaestheticParacetmol,PPI+ Domperidone, Fluoroquinolones and Nitroimidazoles which reveals that a substantial number FDCs prescribed are irrational.

CONCLUSION

CONCLUSION

This study sought to assess the quality of the fixed dose combination in tertiary care hospital showed 64 %(25) of combinations were irrational

It is faithless to expose the patients to the preparations that have no proven safety and efficacy

There is a need for detailed study in this area increase rationality of combinations and to establish the fact.

There is a need for a close scrutiny of FDCs marketed and educating prescribers to use them with caution and great care

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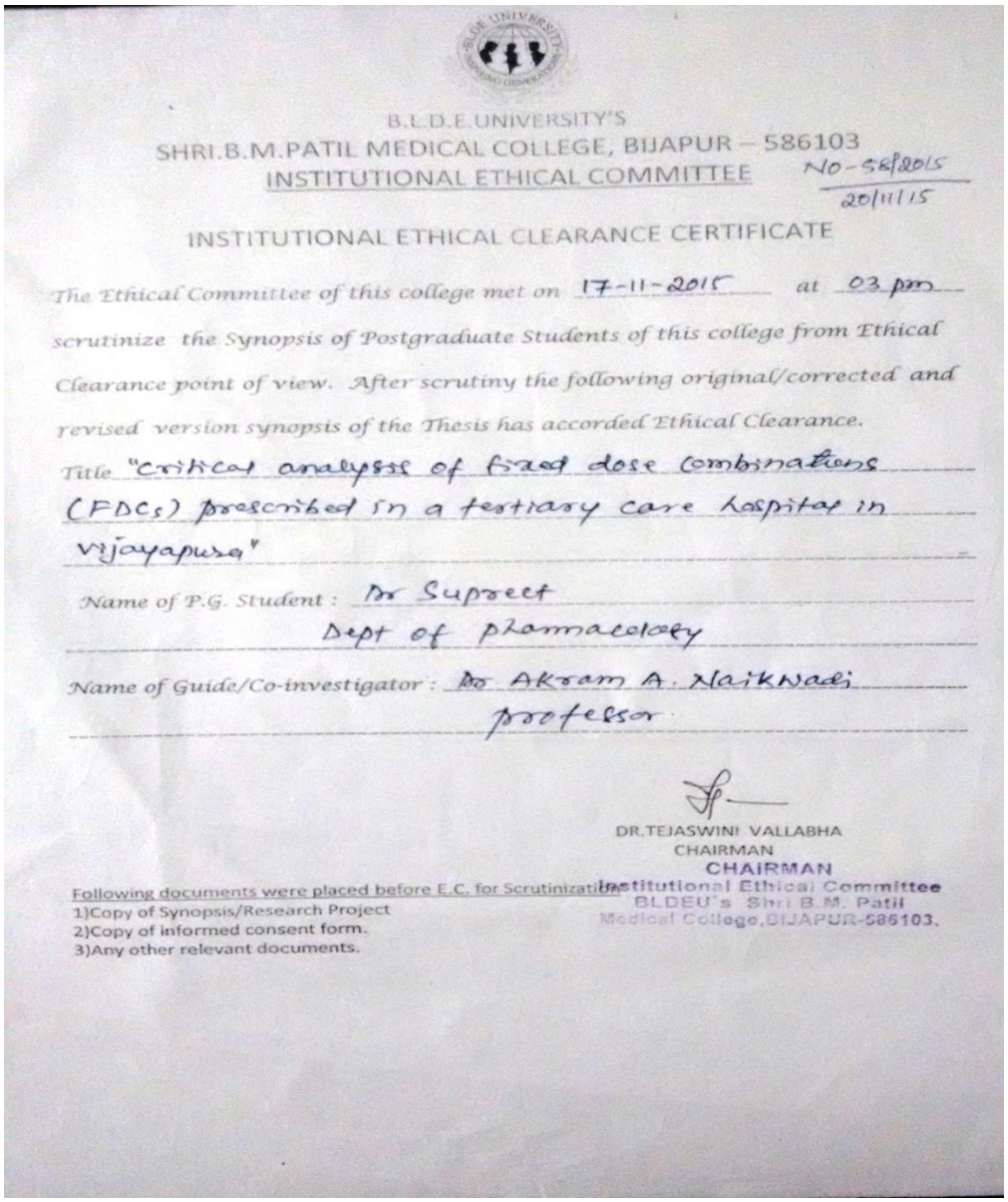
ANNEXURES

ETHICAL CLERANCE CERTIFICATE



B.L.D.E.UNIVERSITY'S
SHRI.B.M.PATIL MEDICAL COLLEGE, BIJAPUR – 586103
INSTITUTIONAL ETHICAL COMMITTEE NO-56/2015
20/11/15

INSTITUTIONAL ETHICAL CLEARANCE CERTIFICATE

The Ethical Committee of this college met on 17-11-2015 at 03 pm scrutinize the Synopsis of Postgraduate Students of this college from Ethical Clearance point of view. After scrutiny the following original/corrected and revised version synopsis of the Thesis has accorded Ethical Clearance.

Title "critical analysis of fixed dose combinations (FDCs) prescribed in a teritiary care hospital in vijayapura"

Name of P.G. Student : Dr Supreet
Dept of pharmacology

Name of Guide/Co-investigator : Dr Akram A. Naikwadi
professor

DR.TEJASWINI VALLABHA
CHAIRMAN
CHAIRMAN
Institutional Ethical Committee
BLDEU's Shri B.M. Patil
Medical College,BIJAPUR-586103.

Following documents were placed before E.C. for Scrutinization
1)Copy of Synopsis/Research Project
2)Copy of informed consent form.
3)Any other relevant documents.

MASTER CHART

		API (Active pharmacological ingredient)		LISTED IN EML		EFFICACY		SAFETY		PHARMA COKINETICS			PHARMACO DYNAMICS		ADVANTAGE OF FDC			SCORE		
SL.No	FDC(Fixed dose combination)	APPROVED BY DCGI	INGREDIENTS BANNED /CONTROVERSTIAL	WHO/NATIONAL/BOTH	NoNE	API	FDC	API	FDC	FAVORABLE	UNFAVORABLE	NoT AFFECTED	SIMILAR	DIFFERENT	REDUCED DOSE	LESS ADR	CONVENIENT	TOTAL	≥7:Rational FDC	≤6: Irrational FDC
		Yes (+1)/No (−1)	Yes (−1)/No (+1)	Yes(+1)	(+0)	Yes (+1)/No (0)	Yes (+1)/No (0)	Yes (+1)/No (0)	Yes (+1)/No (0)	(+1)	(+1)	(+0)	(+1)	(+1)	Yes (+1)/No (0)	Yes (+1)/No (0)	Yes (+1)/No (0)			
1	ISONIAZID +RIFAMPACIN+PYRIZINAMIDE+ ETHAMBUTOL	Yes	No	Yes		Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	No	No	Yes	10	RATIONAL	
2	AMOXICILLIN+CLAVULANIC ACID	Yes	No	Yes		Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	No	No	Yes	10	RATIONAL	
3	PIPERACILLIN +TAZOBACTAM	Yes	No	Yes		Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	No	No	Yes	10	RATIONAL	
4	FERROUS ASCORBATE+ FOLIC ACID	Yes	No	Yes		Yes	Yes	Yes	Yes	No	No	Yes	No	Yes	No	No	Yes	9	RATIONAL	
5	CALCIUM CARBONATE+VITAMIN D3	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	No	No	Yes	9	RATIONAL	
6	CEFTRIAXONE +SALBACTUM	Yes	No	No	Yes	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	No	Yes	7	RATIONAL	
7	TELMISARTAN +AMLODIPINE	Yes	No	No	Yes	Yes	Yes	Yes	No	No	No	Yes	No	Yes	No	No	Yes	7	RATIONAL	
8	CEFUROXIME+CLAVULANIC ACID	Yes	No	No	Yes	Yes	Yes	Yes	No	Yes	No	Yes	No	Yes	No	No	Yes	8	RATIONAL	
9	CEPODOXIME PROXETIL+CLAVULANIC ACID	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	No	No	Yes	8	RATIONAL	
10	AMLODIPINE+HYDROCHLOROTHIZIDE	Yes	No	No	Yes	Yes	Yes	Yes	Yes	No	No	Yes	No	Yes	No	No	Yes	8	RATIONAL	
11	ASPIRIN+CLOPIDOGREL	Yes	No	No	Yes	Yes	Yes	Yes	Yes	No	No	Yes	No	Yes	No	No	Yes	8	RATIONAL	
12	ALBENDAZOLE+IVERMECTIN	Yes	No	No	Yes	Yes	Yes	Yes	No	No	No	Yes	No	Yes	No	No	Yes	7	RATIONAL	
13	TAMSULOSIN+DUTASTERIDE	Yes	No	No	Yes	Yes	Yes	No	Yes	Yes	No	Yes	No	Yes	No	No	Yes	8	RATIONAL	
14	CEFTRIAXONE +TAZOBACTUM	Yes	No	No	Yes	Yes	Yes	Yes	No	Yes	No	Yes	No	Yes	No	No	Yes	7	RATIONAL	

15	CEFIXIME+ ORNIDAZOLE	Yes	No	No	Yes	No	No	No	No	No	No	Yes	No	Yes	No	No	Yes	4		IRRATIONAL
16	OFLOXACIN+ORNIDAZOLE	Yes	No	No	Yes	No	No	No	No	No	No	Yes	No	Yes	No	No	Yes	4		IRRATIONAL
17	PANTOPROZOLE+ DOMPERIDONE	Yes	No	No	Yes	No	No	No	No	No	No	Yes	No	Yes	No	No	Yes	4		IRRATIONAL
18	RABEPROZOLE+DOMPERIDONE	Yes	No	No	Yes	No	No	No	No	No	No	Yes	No	Yes	No	No	Yes	4		IRRATIONAL
19	ACECLOFENAC+TIZANIDINE	Yes	No	No	Yes	No	No	No	No	No	No	Yes	No	Yes	No	No	Yes	4		IRRATIONAL
20	ETORICOXIB+THIOCOLCHICOSIDE	Yes	No	No	Yes	No	No	No	No	No	No	Yes	No	Yes	No	No	Yes	4		IRRATIONAL
21	ACECLOFENAC+THIOCOLCHICOSIDE	Yes	No	No	Yes	No	No	No	No	No	No	Yes	No	Yes	No	No	Yes	4		IRRATIONAL
22	CIPROFLOXACIN+TINIDAZOLE	Yes	No	No	Yes	No	No	No	No	No	No	Yes	No	Yes	No	No	Yes	4		IRRATIONAL
23	ACECLOFENAC+PARACETAMOL	Yes	No	No	Yes	Yes	No	Yes	No	No	No	Yes	No	Yes	No	No	Yes	6		IRRATIONAL
24	PCT+CPM+CAFFEINE+PHENYLEPHRINE	Yes	Yes	No	Yes	No	No	No	No	No	No	Yes	No	Yes	No	No	Yes	2		IRRATIONAL
25	PCT+CPM+GUAIPHENESIN+AMBROXL+ PHENYLEPHRINE	Yes	Yes	No	Yes	No	No	No	No	No	No	Yes	No	Yes	No	No	Yes	2		IRRATIONAL
26	CPM+SODIUM CITRATE+PHENYLEPHRINE+MENTHOL	Yes	Yes	No	Yes	No	No	No	No	No	No	Yes	No	Yes	No	No	Yes	2		IRRATIONAL
27	PCT+CPM+AMBROXL+PHENYLEPHRINE	Yes	Yes	No	Yes	No	No	No	No	No	No	Yes	No	Yes	No	No	Yes	2		IRRATIONAL
28	DICLOFENAC+SERRATIOPEPTIDASE	Yes	No	No	Yes	No	No	No	No	No	No	Yes	No	Yes	No	No	Yes	4		IRRATIONAL
29	DICLOFENAC+SERRATIOPEPTIDASE+PCT	Yes	No	No	Yes	No	No	No	No	No	No	Yes	No	Yes	No	No	Yes	4		IRRATIONAL
30	IBUBRUFEN+PCT	Yes	No	No	Yes	No	No	No	No	No	No	Yes	No	Yes	No	No	Yes	4		IRRATIONAL
31	TRAMADOL +PCT	Yes	No	No	Yes	No	No	No	No	No	No	Yes	No	Yes	No	No	Yes	4		IRRATIONAL
32	MEFINAMIC ACID+PCT	Yes	No	No	Yes	No	No	No	No	No	No	Yes	No	Yes	No	No	Yes	4		IRRATIONAL
33	OFLOXACIN+BECLOMETASONE+ CLOTRIMAZOLE	Yes	No	No	Yes	No	No	No	No	No	No	Yes	No	Yes	No	No	Yes	4		IRRATIONAL
34	CPM+PHENYLEPHRINE+ DEXTROMETHORPHAN HYDROBROMIDE	Yes	Yes	No	Yes	No	No	No	No	No	No	Yes	No	Yes	No	No	Yes	2		IRRATIONAL
35	OFLOXACIN+BECLOMETASONE+ CLOTRIMAZOLE+LIDOCAIN	Yes	No	No	Yes	No	No	No	No	No	No	Yes	No	Yes	No	No	Yes	4		IRRATIONAL
36	MAGALDRATE+SIMETHICONE + OXETACAINE	Yes	No	No	Yes	No	No	No	No	No	No	Yes	No	Yes	No	No	Yes	4		IRRATIONAL
37	OFLOXACIN+DEXTAMETASONE	Yes	No	No	Yes	No	No	No	No	No	No	Yes	No	Yes	No	No	Yes	4		IRRATIONAL
38	CIPROFLOXACIN+DEXTAMETASONE	Yes	No	No	Yes	No	No	No	No	No	No	Yes	No	Yes	No	No	Yes	4		IRRATIONAL
39	SUCRALFATE+OXETACAINE	Yes	No	No	Yes	No	No	No	No	No	No	Yes	No	Yes	No	No	Yes	4		IRRATIONAL