

Review Article

**FIXED DOSE COMBINATION PRODUCTS OF ANTI-HYPERTENSIVE'S AND ANTI-DIABETIC'S -
INDIAN REGULATORY PERSPECTIVE AGAINST USA AND EU**

VARALAKSHMI K*, SUBRAMANIAN G., SUNITHA REDDY M.

Centre for pharmaceutical sciences, IST, JNTUH, Kukatpally, Hyderabad. Email: v.kommineni@yahoo.com

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ABSTRACT

Fixed dose combination (FDC) products are gaining more interest by pharma companies worldwide considering their importance in treating the disease and the increased safety/efficacy profile. Very few general guidelines are available with respect to FDCs in USA whereas Europe has some guidelines while India has just started developing such guidelines. Indian market is flooded with several irrational formulations / combinations, and western markets such as USA and Europe are still very cautious in giving approvals for FDCs. Lack of stringent guidelines, proper approval processes and the strict oversight can be considered as major reasons for such irrational drugs in Indian market.

Keywords: Fixed dose combinations, Anti-diabetics, Anti-hypertensives, Guidelines.

INTRODUCTION

Fixed Dose Combination (FDC) products are medicines that contain two or more active ingredients in a fixed ratio of doses in the same formulation [1, 2]. FDCs are formulated to have a similar bioequivalence of the two agents as separate tablets and therefore have similar pharmacokinetic and pharmacodynamic properties as the separate tablets [3]. FDCs proposed utility in several disciplines of medicine has been based on the premise that they are more convenient, i.e. 'reduce the pill burden', for individuals taking multiple medication and thereby improve adherence or 'concordance' with drug treatment [4, 5, 6]. They may also be used as part of a triple therapy regimen as indicated by separate tablets. The indications, efficacy, tolerability and adverse effects for FDCs are generally the same as for the two active ingredients. Importantly, drug interactions and contraindications must be respected for each component, a situation which has the potential to limit usage in some individuals. By contrast, the use of FDCs may improve the clinical benefit of two drugs at lower doses [7], rather than the use of one drug at a higher dose, as well as reducing the dose-related side effects of a single drug.

FDCs and Diabetes

Diabetes mellitus is a chronic disease that is growing in prevalence worldwide, with the vast majority of those afflicted having T2DM. In 2010, the worldwide prevalence of diabetes was estimated to be 285 million, with almost 90% of diabetic patients having T2DM [8]. This number is expected to grow to 366 million by 2030[9]. A number of barriers to achieving glycemic control targets exist, most notable are complicated dosing regimens, risk of hypoglycemia and risk of weight gain following improved glycemic control[10, 12]. Currently, there are licensed FDCs of oral hyperglycaemic agents, anti-hypertensive agents and hypolipidaemic agents used in Type 2 diabetes. The role of FDCs as first line, second line, or as part of triple (or even quadruple) therapy still requires further assessment [13]. Also, the concept of patient choice in the number of drugs in the management of Type 2 diabetes may be the future for FDCs [13].

While there is now some evidence that FDCs offer a benefit from the point of view of medication adherence and glucose lowering, they may only be suitable for those on a stable, but standard dose, regimen.

FDCs and Hypertension

Many patients require more than one medication to optimally control their blood pressure; two agents of different pharmacologic classes are often effective in achieving this goal [14, 15, 16].

The use of antihypertensive agents to lower blood pressure (BP) decreases the risk of cardiovascular events [17], and greater BP reductions result in improved clinical outcomes [18, 19]. Evidence now suggests that the majority of hypertensives will require combinations of antihypertensive medications to achieve optimal blood pressure control[20, 21, 22, 23]. National Council on Patient Information and Education survey in USA showed that one third of patients receive at least 2 prescriptions and 10% of patients receive 4 or more prescriptions after a visit to a primary care physician [24]. Another study showed that the fixed combinations were generally well tolerated with an increased blood pressure lowering effect as compared with the individual components in patients with stage I to III hypertension[25, 26]. Patient noncompliance is an important contributor to poor blood pressure control. Factors that contribute to noncompliance include side-effect profile, convenience of dosing schedule, cost of medication, and lack of patient education [27]. Also, low-dose, fixed-dose combination therapy allows physicians to prescribe two drugs in one pill and, hence, to improve patient compliance[28].

Hypertension is recognized as a major risk factor for cardiovascular and renal diseases and represents the leading cause of mortality worldwide [29]. Several studies have shown that BP can be reduced by lifestyle/behavior modification. It has been recommended that more emphasis be placed on lifestyle/behavior modification (obesity, high dietary intake of fat and sodium, physical inactivity, smoking, excessive alcohol intake, low dietary potassium intake) to control BP and also to improve the efficacy of pharmacologic treatment of high BP.

New classes of antihypertensive drugs such as aldosterone receptor blockers[30], vasodilator beta-blockers[31,32], renin inhibitors[33,34], endothelin receptor antagonists, and dual endopeptidase inhibitors[35, 36] may become the preferred choice in future. Treatment of human hypertension with vaccines is feasible but is not likely to be available in the near future[37, 38]. Another challenge in hypertension research is, the goal of reducing the devastating target organ damage seen in the brain, kidney, systemic vasculature, and heart as a consequence of uncontrolled hypertension[39, 40, 41, 42].

Advantages & disadvantages of FDC's

Advantages: Drugs that are normally given in combination are more conveniently prescribed and consumed as a Fixed drug combination[43].

FDCs offer simple dosage schedule which improves patient compliance and therefore improves treatment outcomes. This is especially important in elderly patients or patients suffering from multiple disorders[44]. FDCs are more economic than single ingredient drugs[45]. Reduced "pill burden" can greatly enhance the overall patient compliance[46, 47].

Disadvantages: [48] FDCs discourage separate titration of each active ingredient. This is a particular problem when both of the active ingredients require dose titration. When active ingredients have different pharmacokinetics and/or pharmacodynamics, a fixed dose combination may not be appropriate. If one drug is contraindicated for a patient, whole FDC cannot be prescribed. FDCs dosing is inflexible and cannot be regulated to patient's needs

FDCs AND THEIR REGULATIONS/GUIDELINES

There were no specific guidelines available with respect to FDCs in general and antidiabetic FDCs in particular. However, there exists guidance on fixed dose combination and co-packaged drug products for treatment of HIV[49] in USA. Also some guidelines available for antihypertensive FDCs[50] with USFDA. In Europe, there were some guidelines available for FDCs in general and for anti-hypertensives / anti-diabetics in particular. In general guidelines, guidelines on clinical[51] and non-clinical development[52] of FDCs, draft guidelines on FDC products[53] and revised guidelines on clinical development of FDCs regarding dossier requirements[54], were available. In particular, concept paper on FDC products in the treatment of hypertension[55], guidelines on clinical investigation of FDCs in the treatment of hypertension[56] and diabetes mellitus[57] is available for the applicant to have basic understanding about specific requirements with EMEA. There were no specific guidelines with respect to FDCs in general and antidiabetic and antihypertensive FDCs in particular with CDSCO but there exists a description on the various groups in to which FDCs may fall and also the data requirements were described in brief for all the groups[58].

Available guidelines for FDCs in USA

a) Guidance for industry - fixed dose combinations and co packaged drug products for treatment of HIV- 2006[59]; b) Some guidelines are available for anti-hypertensive FDCs such as Principles for clinical evaluation of new antihypertensive drugs -2000[60]. No guidelines are available for anti-diabetics, at all

Available guidelines for FDCs in EU

a) Guideline on the non clinical development of fixed dose combination of medicinal products-2008[61]; b) Draft guidelines on fixed dose combination products-2008[62]; c) Guideline on clinical development of fixed dose combination medicinal products-2009[63]; d) Concept paper on the need to revise the Guideline on the clinical development of fixed dose combinations of medicinal products regarding dossier content requirements - Feb 2013[64]

India - CDSCO Regulations

FDC regulations in India

According to rule 122E of Drug and Cosmetics Rule, a fixed dose combination of two or more drugs is considered to be a new drug. This is because of the fact that by combining two or more drugs, the safety, efficacy, and bioavailability of the individual Active Pharmaceutical Ingredient (API) may change. Permission to import or manufacture of a fixed dose combination is specified in rule 122D.

General considerations

A clear justification with a valid therapeutic rationale of the particular combination of active substances proposed will be the basis of approval.

- It is not always necessary to generate new (original) data. Evidence may be obtained from the scientific literature, subject to its being of adequate quality.

- In case of FDC where all the active ingredients are approved individually, if a Clinical Trial (CT) is required, confirmatory studies to prove efficacy, preferably by parallel group comparisons in which the FDC is compared to its individual substances may be considered. When feasible, a placebo arm may be incorporated. Comparative CTs of the FDC with reference treatment may be necessary, especially when the therapeutic justification talks more on the FDCs superiority over a reference treatment.

Available guidelines for FDCs in India

a) Guidance for industry on fixed dose combinations -2010[65]; b) Policy guidelines for approval of fixed dose combination in India - June 2013[66]; c) CDSCO released several circulars in 2013 on 15thJan, 21stMar, 1stand 5thJuly, 26thAug and 2ndSep 2013 to all state drug controller authorities to ensure all FDC product manufacturers in their concern states should submit the safety and efficacy data to them which have not approved by CDSCO[67], [68], [69], [70], [71]

approval trends in last decade

Antidiabetic and Antihypertensive Drug Approvals

Antidiabetic and antihypertensive fixed dose combination products approved by USFDA, European Commission and Drugs Controller General of India, CDSCO are obtained and compared below. There exist differences in the application forms required to get an approval for medicinal products by respective drug regulatory authorities. Approved drug (Generic or branded drug name), drug approval date, application number and company the drug belongs to were obtained from electronic Orange book from the year 2000 through 2012.

Antidiabetic drugs approved by USFDA

A total of 95 drugs were approved by USFDA for diabetes out of which 21 were FDCs. The year 2005 received maximum number of antidiabetic drug approvals, both single component products (SCPs) (21) and fixed dose combinations (FDCs) (09). The latest FDC drug approved (approval date: 25/01/13) by USFDA for diabetes is Kazano (alogliptin and metformin hydrochloride) tablets, and Oseni (alogliptin and pioglitazone) tablets by Takeda.

Antihypertensive drugs approved by USFDA: In total, 230 antihypertensive drugs were approved by USFDA under section 505 of Federal Food, Drug and Cosmetic Act. Out of 230 approved antihypertensive drugs during 2000-2012, 55 were fixed dose.

Antidiabetic drugs approved by EMA

Brand name, the composition, the company (Marketing Authorization Holder) and the approval date were compiled from EudraPharm from 2000 through 2012. There were a total of 14 antidiabetic drugs given marketing authorization out of which 8 were FDCs and a total of 16 antihypertensive drugs out of which 10 were FDCs. There were no approvals during most of the years.

Antihypertensive Drugs Approved by EMA

There are 12 antihypertensive drugs approved by EMA till 2012 starting 2000.

Drug Approvals in India

[72] [73]: Indian market is flooded with over 80000 formulations. These formulations contain either single drug or more than two drugs in combination (Fixed dose combination). While all formulations are used for the treatment or prevention of one or the other disease, only a few of them are lifesaving and essential[74]. Although there are less number of essential medicines and a few fixed dose combinations in the list of essential medicines, a lot of fixed dose combination formulations are available in the Indian market.

A few combinations are considered to be rational while many others are irrational. Some degree of irresponsibility on the part of pharmaceutical industry and loopholes in approval process has fueled the growth of such irrational combinations[75].

List of drugs approved for marketing in India consists of approvals given by DCGI of a specified strength and formulation or Active Pharmaceutical Ingredient (API) and does not specify the company name. Further once the drugs is been approved any number of companies can apply for the approval for their respective formulation and get their drug approved.

Any company having manufacturing license can market the drug without approval of DCGI once the drug approval date completes 4 years or included in Indian pharmacopoeia. Hence massive numbers of brands are available in the Indian market unlike other countries like US and Europe. The numbers of brands available in the Indian market are discussed further in detail. There were total of 18 antidiabetic drugs in the list of drugs approved for marketing in India approved by Drugs Controller General of India, CDSCO from the year 2000 to 2012, out of which 10 were fixed dose combinations.

There were total of 57 antihypertensive drugs in the list of drugs approved for marketing in India approved by Drugs Controller General of India, CDSCO from the year 2000 to 2012. Out of 57 antihypertensive drugs 38 were fixed dose combinations.

DISCUSSION

No systematic guidelines are available with US, European and Indian regulatory authorities with respect to antidiabetic and antihypertensive FDCs. Approvals were given on case to case basis and available general guidelines for medicinal products with regard to efficacy, quality and safety.

Although general guidelines provide information about the data required to be submitted there exists some categories into which FDCs would fall makes it complex and demand specific requirements for each category. Specific regulatory requirements for approval of antidiabetic and antihypertensive fixed dose combinations: Data requirements for approval of FDC depend up on the category into which the application falls.

BA/BE, preclinical pharmacology, Pk/PD and clinical safety and efficacy; f) GMP status of the manufacturing firm; g) finally, product information and post marketing surveillance. The basic requirements for broad categories are: a) rationale for the combination including balance between advantages and disadvantages; b) its marketing status in other countries; c) literature data analysis; d) developmental studies; e) data such as Data requirements for approval of FDC depend up on the category into which the application falls. However, each application would be considered on its own merits, based on scientific judgment and logical argument.

CONCLUSION

It is evident from the literature that there is an increasing attention towards FDCs among pharmaceutical companies. There is an increasing prevalence of both diabetes and hypertension and the estimated figures are frightening. Guidelines for the management of diabetes and hypertension stress the importance of fixed dose combination therapy both for initiation therapy in some patients and second line therapy in all patients. There is an increasing approval trend of FDCs by regulatory authorities (USFDA, EMEA and CDSCO) when compared to the single component products. This indicates that the regulatory authorities are convinced of approving drug combinations. Antihypertensive therapy in the future or near future should be directed towards improving BP control in treated hypertensive patients with the available drugs by using the right combinations at optimum doses, individually tailored genopolymorphism directed therapy, or development of new modalities such as gene therapy and vaccines. The role of FDCs in therapy and the concept of patient choice in the number of drugs in the management of Type 2 diabetes may be the future for FDCs to develop anti-diabetic FDCs in future.

There are less clear regulatory guidelines with respect to antidiabetic and antihypertensive FDCs. The emergence of irrational FDCs in Indian market has disturbed many stakeholders of pharmaceutical industry.

The issues related irrational combinations are slowly being resolved now due to the active role of DCGI, cooperation from the state licensing authorities and the pharmaceutical companies. Hence, from the present review we can say that fixed dose combinations will continue to be there in the market benefiting the pharmaceutical companies, physicians and the patients. The only possible bottleneck in the way of FDC is the unclear guidelines by the respective authorities which would definitely be clarified in near future.

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