ACCESSING MEDICINES IN AFRICA AND SOUTH ASIA (AMASA)

The Foundation for Research in Community Health

Policy Brief

'Fixed Dose Combination' drugs and the case of Metformin.

'Fixed Dose Combination' (FDC) drugs are formulations comprised of two or more drugs that are combined in a fixed ratio of doses and available in a single dosage form. Their unchecked proliferation poses a threat to public health in India. This case study of FDCs for diabetes treatment shows that the problem is large and multidimensional.

For over three decades, official reports have warned of the widespread flooding of irrational medicines in India. The uncontrolled proliferation of 'Fixed Dose Combination' (FDC) drugs whose safety and efficacy may not have been checked by the regulatory authorities, are a special concern. Metformin, an oral anti-diabetes drug is an example of the unchecked FDC growth.

International and national guidelines do not recommend FDCs for the treatment of diabetes. FDCs do not feature in India's National List of Essential Medicines (NLEM), 2011; or the WHO Model List of Essential Medicines (2011).

Treatment for diabetes is undertaken largely in the private health sector. Since 1987, pilot projects under the 'National Diabetes Control Programme' were initiated in the districts of Jammu and Kashmir, Tamil Nadu and Karnataka. Wider roll out was hampered by the lack of public funding.

FDCs and their regulatory milestones:

The drug regulatory system in India is mainly governed by the much-revised Drugs and Cosmetics Act 1940, and the Drugs and Cosmetics Rules 1945, made and amended by the Central Government. The Central Drugs Standard Control Organisation (CDSCO) must issue pre-marketing approval of 'new drugs' (including FDCs). Manufacturing licenses are thereafter granted by the State regulatory authorities.

FDCs were not expressly referred to in the legislation until 1988, when the Rules were amended to include FDCs within the definition of 'new drugs'. Set out under the Drugs and Cosmetics Rules1988(Eighth Amendment) these rules required pre-marketing approval and specified four categories of FDC for data submission purposes. It was only in 2001 that the Rules required CDSCO to be satisfied that 'new drugs' were safe and effective before giving such approval.

Records of the Drug Controller General (India) show that between 1961 and February 2013, his office approved a total of 1,125 FDC formulations. The first metformin FDC was approved in November 1996. Since then, of the 42 anti-diabetes FDCs approved, 25 are metformin formulations.

Data from 'PharmaTrac' (November 2007 to October 2012) however revealed as many as 1,144 anti-diabetes products in the market. Of these, 575 were FDC and 569 were 'Single Dose Formulations' (SDF). Metformin FDCs comprised 93 per cent (536/575) of the anti-diabetes FDCs and metformin SDFs comprised only 22 per cent (123/569) of the anti-diabetes SDFs.

PARTNERS

http://www.amasa-project.eu/

University of Edinburgh, Edinburgh, UK (Project Coordinator)

The Swiss Tropical and Public Health Institute, Basel, Switzerland

University of Ghent, Ghent, Belgium

Queen Mary University of London, London, UK

Mbarara University of Science and Technology, Mbarara, Uganda

University of the Western Cape, Cape Town, South Africa

Makerere University, Kampala, Uganda

Foundation for Research in Community Health, Mumbai, India

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A survey of 124 retail pharmacies conducted in four districts of Maharashtra by the Foundation for Research in Community Health (FRCH) during January 2012 to June 2012, (within the framework of AMASA project), recorded 56 different metformin products, of which 36 were FDCs and 20 were SDFs.

Analysis of the PharmaTrac data reveals that for six FDC products, regulatory approval and market launch dates were within the same time-frame. In the case of another ten such products, the market launch occurred prior to the date of official approval. Seven FDC products had no record of approval from the apex central regulatory authority, the Central Drugs Standard Control Organisation (CDSCO). This possibly reflects cases where State Authorities granted manufacturing licenses without prior approval of the CDSCO.

In comparison with India, only 11 metformin FDC products are listed by the European Medicines Agency (EMA). Of these four products are listed in the UK's British National Formulary (March, 2013) and Monthly Index of Medical Specialities (MIMS).

The Indian Rules on FDCs and WHO Guidance:

Three differences are identified between the Indian Rules and 'WHO Expert Committee's 2005 Guidance on FDCs'.

(1)The Indian Rules categorise FDCs for data submission purposes. This categorisation is based in part, on the likelihood of significant pharmacodynamic or pharmacokinetic interactions. Such data is required by CDSCO in order to determine safety and efficacy of the drug. The WHO Guidance groups FDCs for these purposes by reference to the prior regulatory consideration of the active ingredients, and so avoids pre-judgment.

(2) In introducing 'convenience' (of patients) as a criterion potentially justifying approval, the Indian Rules have elevated one consideration out of many.

(3) The Indian Rules do not reflect the need to balance both the advantages and disadvantages of FDCs, which the WHO Committee considers "should form a major component of submissions".

Indian data shows that metformin FDCs dominated over metformin SDFs by a ratio of 3:1 between the years 2007-'12. In 2012, metformin FDCs comprised 56% of oral diabetes drugs sold in volume. (Table1).

The sales value of Metformin FDCs rose from 55 per cent in 2007-'08 to 61 per cent of oral diabetes drugs in 2011-'12. In contrast, community dispensing data from England and Australia reveals that metformin FDCs comprise less than four per cent of oral anti-diabetes prescriptions. The prescription value of metformin FDCs was 5 and 9 per cent of the total oral anti-diabetes drugs in these two countries respectively.

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Table1. Proportion of FDCs in anti diabetes drugs used in India, England & Australia

Fixed Dose Combinations (FDCs)	India: Annual sales volumes (millions of units)					Prescriptions (millions)	
	2007-08	2008-09	2009-10	2010-11	2011-12	England 2011	Australia 2010
Metformin FDCs	**234.5**	**286.7**	**333.2**	**394.1**	**455.4**	**0.28**	**0.30**
Diabetes FDCs Total	**237.4**	**289.3**	**336.1**	**396.8**	**457.9**	**0.28**	**0.30**
Metformin SDFs	73.8	96.0	111.2	129.4	148.0	15.60	4.53
Diabetes SDFs Total	238.6	287.3	309.9	332.7	359.2	25.96	7.89
All oral diabetic drugs	**476.0**	**576.6**	**646.0**	**729.5**	**817.1**	**26.24**	**8.19**
A	**49**	**50**	**52**	**54**	**56**	**1.1**	**3.7**
B	**55**	**55**	**57**	**59**	**61**	**5.2**	**8.9**

A - Metformin FDCs as % of sales/prescription volume of all oral diabetic drugs (%), B - Metformin FDCs as % of sales/prescription value of all oral diabetes drugs (%).
Data Sources: India, PharmaTrac data; England NHS Prescription Cost Analysis report 2011, http://www.hscic.gov.uk/searchcatalogue?productid=5461&q=title%3a%22prescription+cost+analysis%22&sort=Relevance&size=10&page=1#top; Australia, Australian Statistics on Medicines report 2010, http://www.pbs.gov.au/info/browse/statistics. 'Sales unit' = 10-tablets/capsules.

A comparison of the average market price of various metformin FDCs and its SDFs show that the former are less. (Table 2) Most of the companies sold metformin FDCs at a lower price (almost half) than the SDFs manufactured by them. (Table 3) Additionally, the same formulation of metformin FDCs available under different brand names in the market reveal a wide variation in price. (Table 2) The sales data shows that the higher priced metformin products have the larger market share.

Table 2. Comparison of average prices of FDCs and SDFs available in the market Source: CIMS ® and MedIndia®

				Price/10 tablets(INR)				
	Drugs	Dose in mg	Num. of brands	Mean	FDC Vs SDF	Median	Min.	Max.
FDC	metformin + glibenclamide	500+5	35	19.9	19.9	16.3	10	37.5
SDF	glibenclamide	5	32	6.57	19.5	5.97	1.95	19.5
SDF	metformin	500	170	12.93		12	6	40
FDC	metformin + glimepiride	500 + 1	92	37.78	37.78	39	11.9	80
SDF	metformin	500	170	12.93	38.54	12	6	40
SDF	glimepiride	1	142	25.61		25	8.9	71.5
FDC	metformin + glimepiride	500 + 2	102	52.48	52.48	49.8	21.98	128
SDF	metformin	500	170	12.93	57.68	12	6	40
SDF	glimepiride	2	142	44.75		43.05	10	125

Table 3. Comparison of price of FDCs and their SDFs by the same manufacturer Source: CIMS ® and MedIndia®

Abbott Healthcare Pvt Ltd	Fixed Dose Combination		Price/10 tablets (INR)	
Brand name	Drug 1	Other drugs	FDC	Sum of SDFs
MELITUS tab	Metformin-500mg	glibenclamide 5 mg	12	23.87
DIABETROL-3P Bilayered- tab	Metformin-500mg	glibenclamide 5 mg, pioglitazone 15mg	54.75	87.83
MINSUGAR-G tab	Metformin-500mg	glimepiride 1mg	34	76.33
TRIBET-1 Bilayered- tab	Metformin-500mg	glimepiride 1mg, pioglitazone 15 mg	61.08	139.83
MINSUGAR-G tab	Metformin-500mg	glimepiride 2mg	49	131.03
PIOZONE-M tab	Metformin-500mg	pioglitazone 30 mg	65.04	102.83
TRIBET FORTE tab	Metformin-500mg	glimepiride 2mg, pioglitazone 15 mg	81.5	195.03
TRIBET-2 Bilayered- tab	Metformin-500mg	glimepiride 2mg, pioglitazone 15 mg	81.66	195.03
DIABETROL tab	Metformin-500mg	glibenclamide 5 mg	22	23.87
GLUFORMIN-G2 tab	Metformin-500mg	glimepiride 2mg	57.94	131.03
OBIMET-GX tab	Metformin-500mg	glimepiride 1mg	43.5	76.33
TRIBET FORTE tab	Metformin-500mg	glimepiride 1mg, pioglitazone 15 mg	73	139.83
OBIMET-GX tab	Metformin-500mg	glimepiride 2mg	59.5	131.03
GLUFORMIN-G1 tab	Metformin-500mg	glimepiride 1mg	44.06	76.33
PIOZONE-M tab	Metformin-500mg	pioglitazone 15 mg	55.46	77.83
DIABETROL SR- tab	Metformin-500mg	glibenclamide 5 mg	29.36	23.87

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Questions:

What was the type of data reviewed by the regulatory authorities before granting approvals to the FDCs?

In contrast to England and Australia, Indian sales data indicates that prescribing practices favour FDCs. There is no evidence that these prescribing practices are clinically rational. Why are they allowed to continue?

By what means does the Central Drugs Standard Control Organisation (CDSCO) -- which clears safety and efficacy data of new drugs – coordinate its list of approvals with the various State units of the Food and Drug Administration (FDA) who then grants manufacturing or import licenses. How is the record keeping shared between the States?

Should the primary Act – The Drugs and Cosmetics Act, 1940 – specify requirements of how CDSCO is to be satisfied about the safety and effectiveness of a new drug (including FDCs)?

Should the categorisation of and data submission requirements for FDCs (currently in Appendix VI of the Rules) not be amended, so that they follow the WHO guidance more closely?

Does the large number of products reflect strong competition among manufacturers? If so, why is the share of the more expensive metformin FDC products in the market higher?

Are the manufacturers ensuring their market share by introducing new products under different brand names, with no therapeutic advantage?

Why do some manufacturers produce the same formulation with different brand names?

Recommendations

- All FDCs need to be evaluated for their safety and efficacy. The government should also review the list of FDCs and limit their numbers to where there is a clear cut medical need.
- The FDC issue highlights the need to strengthen coordination between CDSCO and state level FDAs, to ensure a uniform pattern nationwide. There is need for a central database on drug licenses issued by the different states under generic and brand names. Further data on volume of drugs consumed in the country, their sales value and prescribing practices would clarify the patterns of irrational drug use and help inform policy-making.
- Clear treatment guidelines on the use of FDCs are required for the private healthcare sector; which indicate the circumstances in which they should be prescribed.
- Consumers should have access to the database of all available options for any prescribed drugs. This will empower them to purchase safe and affordable medicines. Measures to monitor the availability of drugs need to be developed and enforced effectively by government.
- Pharmacovigilance in the country needs to be strengthened and data should be placed in the public domain. Regulators should effectively use this data to ensure availability of safe and quality medicines in the market.

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