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Regulation and use of metformin FDCs in India

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Background

Medicines regulatory processes aim to ensure that marketed drugs are effective and safe. In India for over thirty years, parliamentary reports have highlighted a proliferation of 'irrational' medicines, in particular, fixed dose combination (FDC) products. The quality of the underpinning regulatory processes has recently come under intense scrutiny.

In a field study on medicines access, we found that metformin FDCs for diabetes were used more commonly than single drug formulations (SDFs). This was at odds with the national Essential Medicines List and with Indian and international treatment guidelines and possibly reflected regulatory rigour and commercial advantage as much as prescribers' choices. To better understand the situation, we examined regulatory approvals and use in India of metformin FDCs.

Aims

To examine the Indian regulatory framework for FDCs and investigate the use of FDC products taking as an example metformin FDCs for diabetes and comparing use in India with that in England and Australia, countries with tightly controlled regulatory processes.

Objectives

•To determine numbers of approvals granted for metformin FDCs by the national regulator, the Central Drugs Standard Control Organisation (CDSCO).

•To determine the numbers of metformin FDC products available in India and their volumes of use and value as proportions of total oral diabetes drug use.

•To compare metformin FDC products and levels of use in India with England and Australia and compare availability of FDCs manufactured by multi-national companies (MNCs).

Methods

Metformin FDC approvals were determined from CDSCO records. Diabetes oral drug sales information for 5 years, November 2007 – October 2012, was obtained from PharmaTrac, a commercial database of Indian national drug sales. Prescribing data for England were obtained from the National Health Service Prescription Cost Analysis Report for 2011 and for Australia from the Pharmaceutical Benefits Scheme Australian Statistics on Medicines report for 2010.

Results

Metformin FDC approvals in India

Between 1961 and 2012, CDSCO approved 1098 FDC formulations; 45 were for diabetes of which 41 were metformin FDC formulations, 21 original formulations and 20 variants.

Metformin FDC products on the market in India

Pharmatrac listed 1144 branded products for oral treatment of diabetes of which 575 were FDCs. Metformin was included in 536 (93%) corresponding to 23 different formulations. Only 19 formulations had CDSCO approval. Eight were approved before or in the same year as market launch. Eleven had a market launch date that preceded CDSCO approval. Four formulations had no record of CDSCO approval.

Formulations of metformin+glimeperide gave rise to137 branded products; metformin+glicazide,102 products; metformin +pioglitazone, 61;metformin+glibenclamide, 33.

Metformin FDCs available in England and Australia

Five metformin FDC formulations were available in England, four in Australia, each with one branded product on the market.

Sales volumes and value of metformin FDCs

Sales in India of FDCs and SDFs increased annually (Table 1). By 2011-12 metformin FDCs comprised 56% of oral diabetes drug sales volumes. Metformin FDC sales values tripled between 2007 and 2012 and by 2011-12, comprised 61% of the total value of oral diabetes drugs (Table 1).

In England (2011) and Australia (2010), metformin FDCs accounted for under 4% of oral diabetes drugs dispensed in the community and 5% and 9% respectively of their total value (Table 1).

Availability of MNC-manufactured metformin FDCs

Eleven formulations were manufactured and sold in India by MNCs. Of these, only four were available in England and / or Australia (Table 2)

Table 1 Metformin FDCs as a proportion of total volume and value of oral diabetes drugs sold annually in India and dispensed in England (2011) and Australia (2010)

Fixed Dose Combinations (FDCs)	India: Annual sales volumes (millions of units*)					Prescriptions (thousands)	
	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**	**284**	**301**
Other FDCs	2.9	2.6	2.9	2.7	2.5	0	0
Diabetes FDCs Total	**237.4**	**289.3**	**336.1**	**396.8**	**457.9**	**284**	**301**
Single Drug Formulations (SDFs)							
Metformin SDFs	73.8	96.0	111.2	129.4	148.0	15,602	4,533
Other SDFs	164.8	191.4	198.7	203.3	211.3	10,354	3,357
Diabetes SDFs Total	238.6	287.3	309.9	332.7	359.2	25,955	7,890
All oral diabetic drugs	**476.0**	**576.6**	**646.0**	**729.5**	**817.1**	**26,239**	**8,190**
Metformin FDCs as % of sales volume of all oral diabetic drugs	**49%**	**50%**	**52%**	**54%**	**56%**	**1.1%**	**3.7%**

*1 Unit=10 tablets/capsules

Fixed Dose Combinations (FDCs)	India: Annual sales value (millions INR)					Prescription value	
	2007-08	2008-09	2009-10	2010-11	2011-12	England 2011 (thousand £)	Australia 2010 (thousand $)
Metformin FDCs Total	6,797.5	9,053.0	11,601.6	15,224.4	20,115.3	11,888	18,314
Other dibaetes FDCs	132.7	120	134.3	134.6	134.9	nil	nil
Diabetes SDFs Total	5,618.1	7,446.0	8,780.7	10,555.9	12,764.2	216,607	187,114
All oral diabetic drugs	**12,548.3**	**16,619.0**	**20,516.6**	**25,914.9**	**33,014.4**	**228,495**	**205,429**
Metformin FDCs as % of value of all oral diabetes drugs	**55%**	**55%**	**57%**	**59%**	**61%**	**5.2%**	**8.9%**

Table 2 Availability in England and Australia of MNC-manufactured FDCs

FDC formulations available in India manufactured by MNCs: Metformin plus	MNC Manufacturers in India	Available in England	Available in Australia
ACARBOSE	Bayer	No	No
GLIBENCLAMIDE	Abbott, Sanofi Aventis	No	Yes (Alphapharm)
GLIBENCLAMIDE + PIOGLITAZONE	Abbott	No	No
GLICLAZIDE	Abbott, Novartis	No	No
GLIMEPIRIDE	Abbott, Bayer, Glaxo Smith Kline, Merck, Novartis, Pfizer, Sanofi-Aventis	No	No
GLIMEPIRIDE + PIOGLITAZONE	Abbott, Bayer, Pfizer, Sanofi-Aventis	No	No
GLIMEPIRIDE + ATORVASTATIN	Abbott	No	No
PIOGLITAZONE	Abbott, Merck, Sanofi-Aventis,	Yes (Takeda)	No
SITAGLIPTIN	Merck Sharpe Dohme	Yes	Yes
VILDAGLIPTIN	Abbott, Novartis	Yes	Yes (Novartis)
VOGLIBOSE	Abbott, Astra Zeneca, Novartis, Sanofi-Aventis	No	No

Conclusions

Our findings suggest deficient regulation in India of metformin FDCs. Some formulations were marketed apparently without CDSCO approval while many were marketed before approval implying safety and efficacy were not assessed well or even at all. Nevertheless and in the absence of recommendations for their use, FDCs dominate oral diabetes drugs sales. This contrasts with England and Australia where SDFs prevail. MNCs sell products in India for which they have not sought approval in England or Australia suggesting both regulatory deficiency and commercial advantage are drivers of India's high metformin FDC use.

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