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AN EVALUATION OF PACKAGE INSERTS OF ANTIMICROBIAL AGENTS MARKETED IN INDIA

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ABSTRACT

PI (n=123) of marketed AMA were collected over 6 months period. Quality of information presented was assessed and scores were given for adherence to Indian i.e. Schedule D of Drugs and Cosmetics Rules, 1945 (DCR) of India (0- 20) and US guidelines (0- 35). Adequate font size was printed in 50% PI. Only 4% PI were complete as per DCR. Adequate information on contra-indications (25%), use during pregnancy/lactation (82%), warning/precautions (92%), drug-drug (59%) and drug-food interactions (36%), adverse drug reactions (61%), effect on ability to drive/use machines (17%), overdosage (36%), uses (48%), pharmacodynamic (32%) and pharmacokinetic properties (61%), use in children (80%) and elderly (52%), preclinical study data (33%), post-marketing surveillance data (7%), references (12%), recent major changes (10%) and patient counseling information (16%) was included in few PI. A more meticulous approach in preparation of PI to include approved, essential, accurate, evidence-based and updated prescribing information is needed.

Keywords: package inserts, prescribing information, antimicrobial agents prescription

INTRODUCTION

Package insert (PI), also known as Prescription Drug Label or Prescribing Information or Package Circular, is an officially approved printed leaflet accompanying marketed drug products.[1] Apart from being a legal formality, it is a tool primarily intended to guide the prescribers for safe and effective use of the respective drug. The PI is compiled and distributed by the drug manufacturer after regulatory review and approval. Ideally, it must contain the approved, essential, accurate, evidence- based and timely updated information about the drug and should be written in a language that is not promotional, false or misleading.[1] Since it is readily available with the drug product and is mandated to strict regulations, it can be used as a reliable source of information by the prescribers [2 – 5] and can in turn minimize medication errors.[6] These are also one of the important tools in educating consumers and in improving compliance to therapy.[7] In India, regulations for manufacture, import, distribution, and sale of pharmaceutical products are outlined in the "Drugs and Cosmetics Act (DCA) (1940) and Rules (1945)". 'Section 6.2' of 'Schedule D (II)' of the Rules pertains to labeling and packaging information of drugs and specifies that a PI should be written in English language and the required information should be provided under suitable headings (such as posology and method of drug administration, contra- indications, special warnings and special precautions for use(if any), interaction(s) with other medicines and food, use in pregnancy and lactation, effects on ability to drive and use machines, undesirable effects or side effects, and the antidote for overdosing).[8]

Studies show that often PI provide extensive information, displayed in a complex manner, which is neither adequate nor does it conform to the WHO recommendations.[9 – 13] This makes it difficult for readers (prescribers and/or patients) to comprehend and retain the information. Additionally, the prescribing information contained may be out-of-date. In order to minimize medication errors, the US

FDA revised the rules for submission of PI in June 2006 which state that the information in PI should be divided into 3 sections i.e. highlights of prescribing information, contents of the full prescribing information (FPI), and the FPI. [1, 14] Proper references should be quoted for the source of information. The highlights section is a half-page summary of the information that is most important for prescribers. The contents section serves as a navigational tool that references all the sections in the FPI. FPI section should describe in detail the information provided in highlight section along with additional information and every PI must contain patient counseling information.

Considering the fact that AMAs are frequently prescribed medicines, we evaluated the PI of anti-microbial agents (AMA) marketed in India in this study. The development of antimicrobial resistance and the therapeutic failure of AMAs are one of the well recognized problems, which can be partly attributed to non compliance to therapy and irrational use of these drugs. Hence, the PI of this group of drugs must provide good quality information to prescribing physicians. In the present study, PI of AMA were considered a representative sample of PI of all the currently marketed drugs in India. The study aimed to evaluate whether the package inserts of AMAs currently marketed in India fulfilled the criteria laid down by Drugs and Cosmetics Rules of India in terms of parameters of completeness and quality of information. Additionally the study also evaluates whether these parameters meet the requirements specified by the U.S. FDA.

MATERIALS AND METHODS

All PI of AMAs dispensed during the study period of 6 months from five busy pharmacy stores located in a city in Western India were included in the study. A list of all the pharmacy stores located in the city was drawn from the office of pharmacy association of the city. Then, we divided the city into five different zones and made a list of five busy pharmacy stores that dispensed maximum number of prescription drugs and served 24hrs a day in each zone from the list. Then by randomization, one such store was enrolled from each zone. The investigator visited each pharmacy store once a week for one hour and collected all the available PI of AMAs dispensed during this period. Care was taken to identify and exclude duplication of a PI. All of the PI were thoroughly read and interpreted. In the first step, it was evaluated whether the required information (as per DCA and U.S. FDA) was included in the PI or not. Information contained under each of the sections contained in the PI was judged and its accuracy assessed in comparison to that provided in standard textbooks of Pharmacology (Basic and Clinical Pharmacology, Bertram G. Katzung; 11th edition and Goodman & Gilman's the Pharmacological basis of Therapeutics; 11th edition). Following which, the information provided in each head was scrutinized and scored on a predetermined scale of 0 to 3 (Table 1). The scale was constructed in a manner that it reflects the presence of essential information in the PI. For example, the safety sections like warnings and contraindications, adverse effects, etc were given more importance over other sections in lieu of the growing safety concerns with newly marketed drugs. At the same time, requirements of regulatory authorities like DCGI and US FDA was also taken into consideration while devising the scale. US FDA requirements are more stringent and necessitates more detailing (eg- information about post marketing experience) as compared to Indian regulations. Hence, two different scores were decided with respect to requirements of both the countries.

Absence of information was scored "0" and presence of adequate and accurate information was scored 1 – 3 depending on its completeness and accuracy. The total score for each PI was calculated for adherence to DCA (maximum score of 20) and US FDA guidelines (maximum score of 35) separately. Data was analyzed using new graph pad software (INSTAT, version 3) and Microsoft Excel 2007 sheet.

RESULTS

A total of 437 PI were collected. The 314 duplicate PI were excluded and the remaining 123 PI were evaluated. These 123 PI were marketed by 48 national and international pharmaceutical companies in India. Of the total 123 PI studied, 55 were for parenteral preparations, 40 for oral, 19 for topical and 9 were for miscellaneous drug formulations. Majority of these PI lacked a structured layout and uniformity of presentation of information. The overall design of the PI was different from one company to another and even between different medications of the same company. The information was clear, to the point and neatly presented in 8 PI. The font size was less than 9 in 20 PI, 9 or 10 in 41 PI and more than 10 in 62 PI. All the analyzed PI used a white background with black (117), blue (4), or green (2) colored fonts. Five of the PI carried illustrations of the pharmacokinetics of the drug. Two of the PI provided illustrations for patient's education, for example-method of insertion of vaginal clotrimazole tablet. In 6 of the PI, the "warning" section was clearly

highlighted (as a boxed warning and/or printed in capital letters). However, a few deficiencies were observed. For example certain information was found to be contradictory or incongruent at different places in the same leaflet in 7 PI (for example, use of arteether was mentioned as "contraindicated" and "use with caution" under different headings in the same leaflet). In 5 PI, the information was found to be incorrect (for example – in a PI of artesunate, the warning section was incorrect, in another PI,dose of Amoxicillin + clavulanic acid was incorrect and drug interaction information for ceftriaxone was incorrect). The information was speculative or promotional in 2 out of 123 PI. It was observed that the information provided was repeated in different headings of the same leaflet in 85 PI (for example, information on use of AMAs in pediatric patients was frequently repeated under headings of "warnings" and "method of use"). Moreover, it was not clarified whether the PI were directed only at the physicians or at the patients as well.

An evaluation of adherence of PI to DCA of India showed that5 (4.6%) PI provided all the necessary information (i.e. scored 20/20) (Figure 1). Half of PI (n = 62, 50%) scored more than 16/20 and 15 PI (12%) scored less than 10. As per US FDA guidelines, a PI must contain additional detailed information (i.e. besides the requirements specified by DCA of India) (Table 1). While adherence to US FDA guidelines for PI marketed in India is not compulsory, we also evaluated the PI in reference to these guidelines. Out of a total score of 35, 29 PI (23%) scored more than 26 and 2 (1.6%) PI scored more than 30 (Figure 2).The generic name of the drug was provided in all PI (Table 2). Posology of the product was correctly mentioned in 122 (99%) PI. The dose and method of administration of the product was correctly stated in 95(77.2%) PI. Information on indications and use of the product was correctly mentioned in 59(48%). Adequate information on pharmacodynamic and pharmacokinetic properties were present in 39(31.7%) and 75(61%) PI respectively. Contraindications were clearly mentioned in 31 (25.2%) PI. The suitability of use during pregnancy and lactation was specified clearly in 101 (82%) PI, while its suitability in pediatric and geriatric population was mentioned in 98(80%) and 64(52%) PI respectively. Warning and precautions were correctly provided in 113 (92%) of PI. Complete information about interactions of the product with drugs and food (or other substances) was provided in 73 (59.3%) and 45(36.5%) of PI respectively. Information on undesirable effects or side effects or Adverse Drug Reactions was adequate in 75(61%). Effects on ability to drive and use machine was provided in only 21 (17%). All the PI lacked information about abuse or dependence liability of the product. Correct information on overdosage and antidotes for the product was present in 45(36.5%) PI. Data about preclinical study or non-clinical toxicology was present in 41(33.3%) of PI. Information about post- marketing surveillance or clinical studies of the product was provided in 9 (7.3%) of PI. Only 15(12%) PI contained references from authentic literature sources. Recent advances in research were included in 13(10.5%) PI. All the PI lacked information about date of approval of the product. Twenty (16%) PI mentioned information for counseling the patients about the use of the product.

DISCUSSION

Package insert is an officially approved, printed leaflet accompanying marketed drug products, intended to be a tool to guide the prescribers for safe and effective use of the drug.[21,22, 23, 24, 25] It is used by prescribers to gather drug related information and is governed by strict regulations. Hence it is important that they contain accurate and complete information. This study was designed to evaluate the content and quality of information provided in the package inserts of currently marketed antimicrobial agents in India and to identify the deficiencies, if any. AMA were chosen as the representative group of PI since they are a commonly prescribed group of drugs, and prone to misuse. PI, if prepared and used correctly have a potential to minimize this misuse.

A variety of oral and parenteral formulations were dispensed. Font size was legible (more than 9 points) in most PI although bigger font size is recommended for better readability. According to a German study, font size of 9 point is ideal and legible and therefore should be recommended for package inserts.[15] However, other studies suggest that readability is improved when a font size of up to 11 points is used.[16, 17, 18] Certain PI displayed information attractively with the help of graphs and illustrations. However, some PI contained incomplete or incorrect information, or gave inadequate emphasis on important information. For example, effects on ability to drive or use machines, interactions of drug with other drugs (or food) and over-dosage and antidote for drug was neglected in some of the PI. Information regarding contraindications, undesirable or side effects or adverse drug reactions associated with the use of drug was insufficient and confusing in some cases. In a study carried out in India, an analysis of PI (n = 80) demonstrated that the information on the most frequent adverse drug reactions associated with the drug (6.2%) and use of

the drug in pediatric (44%) and geriatric populations was largely missing (13%).[11] Likewise, a study carried out in Palestine, evaluated and compared the patient package inserts of the anti-infective agents manufactured in Palestine with the imported equivalents; package inserts from locally manufactured products had significantly lesser information with respect to warnings, dosage and administration, side effects, clinical pharmacology, date of last revision than those of imported products. Another study from Saudi Arabia evaluated the correctness and completeness of information regarding indications, dosage, cautions or contraindications, side effects and drug interactions in 37 package inserts and observed that substantial disagreement exists in information between generic package inserts versus the British National Formulary and the package insert of the brand product marketed in Saudi Arabia.[19] Similarly, an investigation of 68 patient's PI from frequently used 20 medicines in Germany revealed that many lacked key safety information, including information on daily maximum dose and adverse effects, or had information that was difficult to comprehend.[16]

The US FDA has designed new labeling guidelines in the year 2006 to help health care practitioners easily find, read, and convey information important for the safe and effective use of prescription drugs. The guideline recommends a uniform format for a PI. In the present study, such a structured layout was missing. We also observed that the completeness and quality of information provided in the PI was deficient with respect to the US FDA. All the PI lacked information regarding the abuse potential of the drug and date of approval of the product. Also, majority of PI were found to be deficient in providing non-clinical toxicological and post – marketing surveillance data and few contained references, patient counseling information and information on recent research of the product. This additional information may help make better therapeutic decisions. Hence, though not mandatory as per current regulations, these may be included in the PI in India as well. Improvement in the accuracy and quality of information contained in the package inserts is possible by self-regulation by the industry and by updating and enforcing them periodically. The regulatory authorities in India could strengthen collaboration and information interchange with international agencies to maintain quality standards for delivering information through these package inserts. The availability of a comprehensive database for the DCGI - approved package inserts in India, would be of much help in this direction. Medication compliance can be improved by improving the awareness of patients about their medications.[20] Also, there is a need for 'Patient-oriented Package Insert' in India.

Thus the results of the study indicate that information on safe and appropriate use of medications was not uniformly provided in the PI of AMAs marketed in India. We recommend improvement in content and design of the PI and a strict enforcement of the regulatory guidelines. As package inserts are one of the frequently used sources of drug information by prescribers, their accuracy and completeness is important. AMAs being a commonly prescribed group of drugs and the regulatory recommendations being similar for all marketed drugs, the findings of this study could be extrapolated to other drugs as well.

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CONFLICT OF INTEREST

The authors have no conflict of interest to declare relevant to the contents of this study. No external source of funding has been obtained for the study.

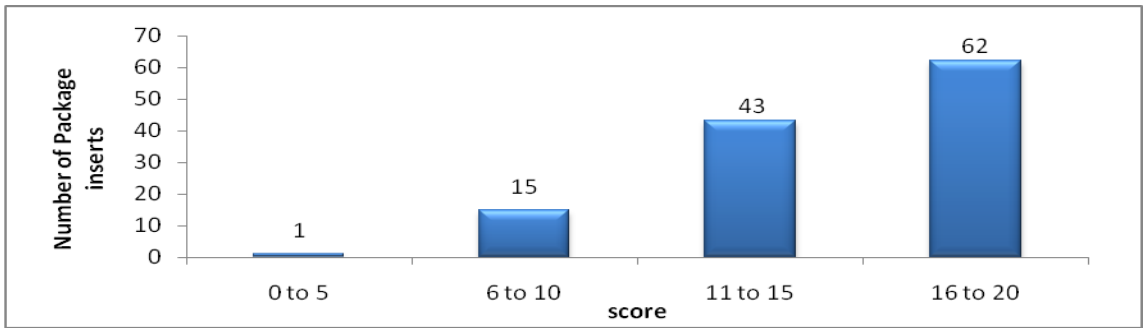

Figure 1: Evaluation of package inserts of AMAs (n = 123) for adherence to Drugs and Cosmetics Act of India

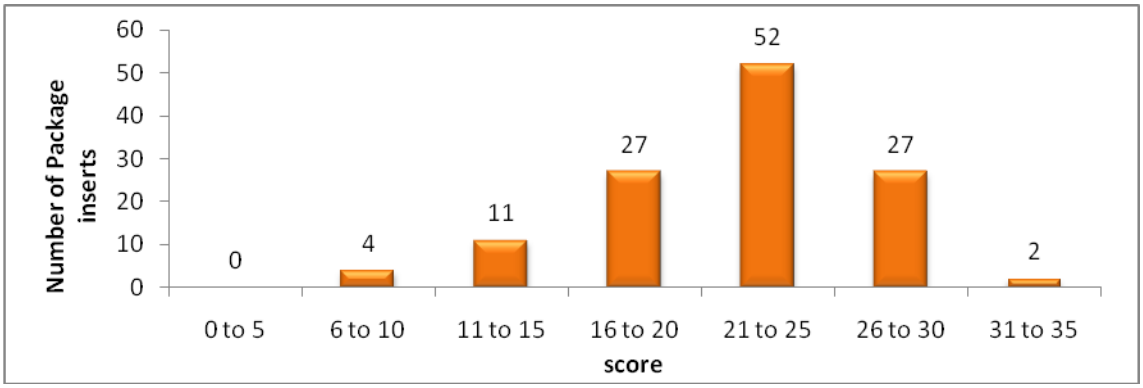

Figure 2: Evaluation of package inserts of AMAs (n = 123) for adherence to US FDA criteria

Table 1: Scoring criteria used in the evaluation of package inserts

Sr. No.	Item	As per DCA guidelines	As per FDA guidelines
1	Generic name of the product	0-1	0-1
2	Dosage form & strength (posology)	0-2	0-2
3	Dose & Method of administration	0-3	0-3
4	Indications & uses	Not applicable	0-3
5	Pharmacodynamic properties	Not applicable	0-2
6	Pharmacokinetic properties	Not applicable	0-2
7	Contra indications	0-2	0-2
8	Use in pregnancy & lactation	0-2	0-2
9	Use in paediatric population	Not applicable	0-1
10	Use in geriatric population	Not applicable	0-1
11	Warnings & precautions	0-1	0-1
12	Interactions with other drugs	0-2	0-2
13	Interactions with food/other substances	0-1	0-1
14	Undesirable effects/SE/ADR	0-3	0-3
15	Effects on ability to drive & use machines, if contra- indicated	0-1	Not applicable
16	Abuse/ dependence property	Not applicable	0-1
17	Overdosage & antidote	0-2	0-2
18	Non- clinical toxicology data or preclinical study data	Not applicable	0-1
19	Clinical study data (post- marketing surveillance)	Not applicable	0-1
20	References made	Not applicable	0-1
21	Recent major changes	Not applicable	0-1
22	Date of approval	Not applicable	0-1
23	Patient counseling information	Not applicable	0-1
	Total	**20**	**35**

Table 2: Occurrences of essential parameters in marketed package inserts of AMA (n = 123) as per DCA and US FDA criteria

Parameters	Number of PI providing complete information		Number of PI providing incomplete information		Number of PI providing no information	
	DCA	US FDA	DCA	US FDA	DCA	US FDA
Generic name of the product	123 (100)	123 (100)	0	0	0	0
Dosage form & strength	122(99)	122(99)	1(0.8)	1(0.8)	0	0
Dose & method of administration	95(77)	95(77)	25(20)	25(20)	3(2)	3(2)
Indications & uses	NA	59(47)	NA	64(52)	NA	0
Pharmacodynamic properties	NA	39(31)	NA	67(54)	NA	17(14)
Pharmacokinetic properties	NA	75(60)	NA	22(17)	NA	26(21)
Contra- indications	31(25)	31(25)	85(69)	85(69)	7(5)	7(5)
Use in pregnancy & lactation	101(82)	101(82)	9(7)	9(7)	13(10)	13(10)
Use in paediatric population	NA	98(79)	NA	-	NA	25(20)
Use in geriatric population	NA	64(52)	NA	-	NA	59(48)
Warnings & precautions	113(91)	113(91)	0	0	10(8)	10(8)
Interactions with other drugs	73(59)	73(59)	23(18)	23(18)	27(22)	27(22)
Interactions with food/other substances	45(36)	45(36)	0	0	78(63)	78(63)
Undesirable /side effects /ADRs	75(60)	75(60)	41(33)	41(33)	7(5.)	7(5)
Effect(s) on ability to drive & use machines	21(17)	NA	-	NA	102(82)	NA
Abuse/ dependence potential	NA	0	NA	0	NA	123(100)
Overdosage & antidote	45(36)	45(36)	34(27)	34(27)	44(35)	44(35)
Nonclinical toxicology or preclinical study data	NA	41(33)	NA	-	NA	82(66)
Clinical study data/post- marketing surveillance	NA	9(7)	NA	-	NA	114(92)
References	NA	15(12)	NA	-	NA	108(87.8)
Recent major changes	NA	13(10)	NA	-	NA	110(89)
Date of approval	NA	0	NA	0	NA	123(100)
Patient counseling information	NA	20(16)	NA	-	NA	103(83)

Numbers in parenthesis indicates percentages

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