PATENT PROTECTION POLICY OF THE THERAPEUTIC GROUP ANGIOTENSIN II RECEPTOR ANTAGONISTS

M. Manova[1], A. Stoimenova[1], L. Peikova[2], P. Peikov[2] and G. Petrova[1]

Faculty of Pharmacy, Medical University – Sofia
[1]Department of Social Pharmacy and Pharmacoeconomics
[2]Department of Pharmaceutical Chemistry

Summary. The goal of the current study is to analyze the patent protection status of medical products included in the therapeutic class angiotensin II receptor antagonists or sartans. The analysis covered the period 1995-2008. A three – step internet patent database search methodology was applied in searching EPO, Orange book and Patent watch. Applications were systematised per IPC code, territory, manufacturer and date of patent issuing. The patent activity depends on the time of expiration of the main patent. The highest number of patents granted for IPC class A61K is due to the fact that this class is related with the therapeutic possibility of the formulations. Per territory protection activity is similar in regard to the prefered countries and follows the market dynamics. For some of the products additional factors might play an important role. Our study shows that a variety of factors are influencing the patent protection policy, such as the time of discovery, product application, disease priority, technologies etc. It appears that the therapeutic competition is more important than the generic one related to establishment of patent profile of particular INN. This is in contrast with the beliefs that the patent protection policy affects mainly generic companies.

Key words: *Angiotensin II receptor antagonists, patent protection, patent policy*

INTRODUCTION

Original medicinal products ensure a new therapeutic option for poorly treated conditions or diseases, while the generic medicines support the sustainability of healthcare provision and contribute to maintaining a control over the pharmaceutical expenditures. The patent protection policy of pharmaceutical manufacturers is a critical milestone for both types of manufactur-

ers (innovative or generic) in terms of market penetration, product lifecycle and patients' access to effective and affordable medicines [1, 2, 3].

After the endorsement of the TRIPS agreement, the influence of the pharmaceuticals patent protection policy on peoples' access to medicines started to be widely discussed in the pharmaceutical literature [4, 5].

Researchers are studying the pharmaceuticals patent protection policy from different aspects. Some are trying to evaluate the real life protection of the basic patent. Others are studying the patent policy of the companies or differences among the countries and their influence on the generic entries [6, 7]. Lots of studies are focusing on the effect of the generic medicines entry on the pricing and reimbursement of medicines [8, 9], and on the utilization of medicines after the patent expiration [10, 11].

The public health concerns lead to the introduction of a measure to make access to patented medicines more flexible [12]. Researchers from the WHO published series of articles on the implementation of TRIPS agreement in the developing countries with the aim to promote series of measures for encouraging the compulsory licensing, exemptions from TRIPS in the national legislation, generic manufacturing and measures that support the generic medicines dispensing [13, 14. 15, 16]. The systematic analysis of the changes in the patent legislation is permanently ongoing and professionals are advocating for better public health through the measures facilitating the access to medicines. This is one of the key tasks for generic pharmaceutical industry and international organizations [17, 18, 19].

The other key task is the analysis of the patent drug policy of originating companies and their influence on generic pharmaceutical industry. Some studies consider that the generic pharmaceutical industry is characterized by a simultaneous entry, rather than sequential [20]. Thus for the generic pharmaceutical companies it is more attractive being the first entering the market. The mathematical models have been created to calculate the aggregated demand and supply features influencing the generic medicines market [21].

From the pharmaceutical perspective, the real life of a new medicine starts after the establishment of its therapeutic posology during the clinical trials and granting the international non-proprietary name (INN) through the World Health Organisation (WHO) procedures [22]. Before that, the product is not recognized by the pharmaceutical companies as a potential competitor due to usage of coded names instead of the INN. Due to this fact, the patent search and detection of any additional protection policy of the originator or therapeutic competitors is sometime complicated and not pharmaceutically reasonable.

During the last three decades a tremendous progress has been made in the hypertension therapy through the introduction of new therapeutic classes [23, 24]. The discovery of a variety of new molecules from the groups of ACE inhibitors and

angiotensin II receptor antagonists or sartanes empowered the physicians in their attempts to attack the complex cardiovascular events in various ways. The fast development of new molecules has led to the development of whole new drug families and increased the competitiveness, thus posing challenges in front of the originator and generic manufacturers to create sophisticated patent protection on one side, and penetrate quickly the market and increase patients' access to low – priced generics, on the other [25, 26, 27].

The goal of the current study is to analyze at a worldwide level the patent protection status of the medicines in the therapeutic class of angiotensin II receptor antagonists and respective patent strategies for the period 1995-2008.

The main questions, discussed in this study are as follows:

1. What types of companies (originators and generics) are claiming the patents for the INNs from the observed groups? Is there any difference among the originators and generics companies patents claims?
2. What is the intensity of patent policy before and after the first patent expiration?
3. What is the specificity of the patent policy according to the IPC classification and territory? What is the time lag for the appearance of the first therapeutic competitors' patent claims within the observed groups of medicines?

MATERIALS AND METHODS

The three three-step step internet patent database search methodology was applied for publications during the period 1995-2008.

The first step was searching the "Orange book" for clarifying the date of issuing of the first patent [28] and "Drug patent watch" database for checking the date of valid patents expiration [29].

The second step was searching the worldwide patent database via the options provided in the European patent database [30] (EPO) by using as a key word the INNs of the observed medicines in the therapeutic group. The third search step was an expanded search via INPADOC patent family system of the European database for clarifying the additional publications of the patents per territory. The INPADOC system connects EPO with more than 70 countries and legal status data for more than 40 patent authorities.

The information for the appearing patents was then systematized according to the following criteria: description title of the patent, inventor, applicant, IPC class, publication number of patent/publication date, and all INPADOC publications connected with the first description title.

Out of all INNs we considered those with valid main patents that were not expired till the beginning of 1990, as well as those new products that are still under clinical trials investigation. Candesartan and olmesartan were not included in the analysis due to their latter appearance in the therapeutic group (Table 1).

Table 1. Patents claims per observed INNs

Therapeutic Group	INN	Number of patents in the worldwide database	Number of patents after the INPADOC search
Sartans	eprosartan	25	50
	losartan	44	100
	valsartan	50	152
	irbesartan	31	48
	telmisartan	44	94

The collected information was analyzed by classifying the patents according to the IPC classification code in following groups – formulation patents (C07D – chemical active substance), formulation or process patents chemical or pharmaceutical technology (C07C, C07D, C07K, C07F, C12K), application patents (A61K – preparations for medical dental or toilet purposes), therapeutic activity (A61P-therapeutic activity of medicinal preparations or chemical compounds). Most of the patents are for more than one IPC code or subgroup due to the complexity of structures or process.

For all patents the year of first publication was compared with the year of the first patent issued, territory covered, and date of patent expiration for particular INN.

RESULTS

Angiotensin receptor blockers (ARBs), also known as angiotensin II receptor antagonists or sartanes, modulate the renin-angiotensin-aldosterone system and thus decrease the blood pressure.

The tetrazole group is a main part of the chemical structure of losartan, irbesartan, olmesartan, candesartan and valsartan. In addition, losartan, irbesartan, olmesartan, candesartan, and telmisartan include one or two imidazole groups [31, 32].

Sartanes patent policy

Historically, within the group of sartanes, the first patent was granted to eprosartan, followed by losartan, valsartan, irbesartan, and telmisartan. The time lag for the next therapeutic alternatives and the time lag for next therapeutic competitor appearance is very short (7 days to 1 year and 9 months), as shown in Table 1.

Twenty five patents were obtained for eprosartan during the studied period. Out of them, 17 were the originator company patents, covering a variety of innovations in the field of chemical composition and process for production (n = 4), area of application (n = 16) and therapeutic activity (n = 5). The first patent from generic manufacturer was obtained during 2006 (IPC-A61K, application), 16 years after the first patent granted. Three other generic companies own patents for the application, obtained during 2006-2008, and two other for novel formulation and process of production.

Losartan's first patent was granted 1 year and 7 months after eprosartan's first patent. Out of 44 patents for losartan, 14% (n = 6) were from the originator Merck&Co, and 86% (n = 38) from the generic companies. There were 3 originator patents for formulation or process; 6 for application, and 1 for therapeutic activity respectively, including overlapping claims for more than one IPC category. The fist patent claim from generic company appears in 2001 (11 year after the first patent was granted) and it was for formulation, process, application, and therapeutic use. Among the patents from generic companies prevail those for application (A61K – 68%), followed by formulation or process (C – 50%) and therapeutic activity (A61P – 24%) claims. The total percentage is higher than 100%, because some patents are for several IPC categories.

Valsartan is the molecule, protected with the highest number of patents despite of the fact that it is not the first one discovered, but probably is the most used one during the investigated period. The first patent for valsartan appears in 1992 and covers 3 areas of protection: formulation, application and therapeutic activity. Ciba Geigy (the company marketed the product first) owns 5 patents (2 for formulation and process, 5 for application and 1 for therapeutic activity). For some areas of protection more than one patent is granted. After the merge with Novartis, 25 patents were issued on the basis of the company claims (2 for process and formulation, 15 for application and 3 for therapeutic activity). Some of these patents are for valsartan combinations, since 2003. The first patent issued to generic companies appears in 2002 for application.

Similar is the case with irbesartan, where the first patent belongs to Bristol Myers (for formulation and application) and after the agreement with Sanofi for joint marketing cooperation, the patent policy became the priority of both companies. Sanofi has been granted on total of 7 patents (4 for application and 2 for therapeutic activity). All other patents are granted to generic companies and 14 of them are formulation or production process patents, 12 for application and 6 for therapeutic activity. First generic competitor patent was granted in 2003 for application and therapeutic activity.

Telmisartan first patent was issued in 1994 year to Boehringer Ingelheim, possessing 22 patents for this INN (6 for formulation or production process, 14 for application and 6 for therapeutic activity). The first patent for generic producer became available in 1999 for benzimidasole containing medicaments and process for preparation.

Typically for the group, the patents are granted either for therapeutic activity or application, very often combined with diuretics, produced by other innovators, owners of the patents. All of the patents are protected with European patents, USA, Australian patents and countries out of the WTO.

The intensity of patent protection policy for the analysed INNs within the group is presented in Figure 1. During the first five years, the patent activity was slow and

started to increase tremendously around the time of expiration of the first patent granted. The only exclusion is losartan due to the fact that it is already with expired main patents.

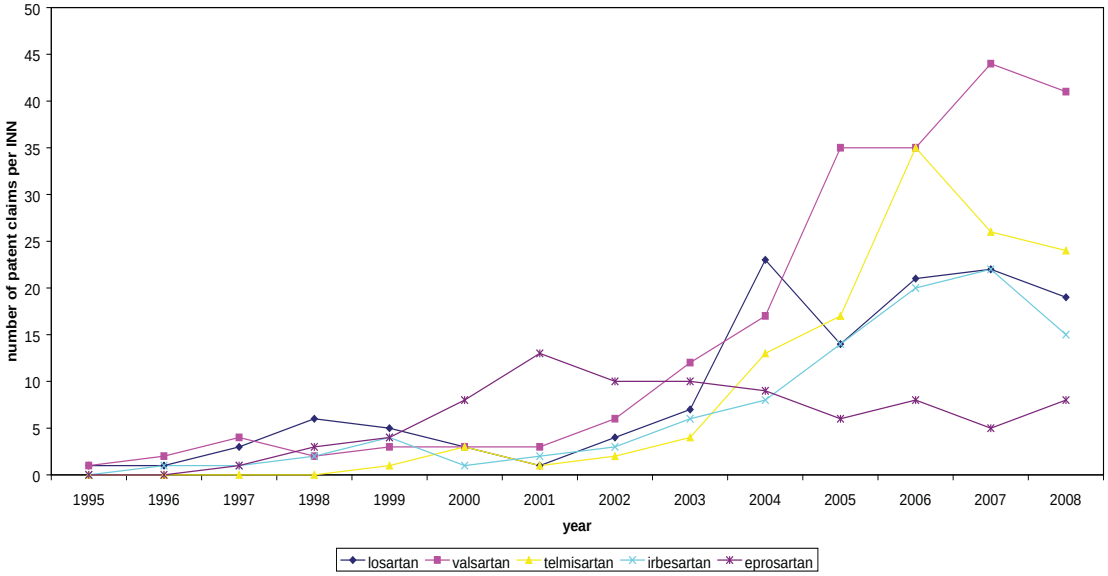

Fig. 1. The intensity of patent protection policy for the observed sartans

Within sartanes group, 20 to 42 patents were granted for application (A61K), 5 to 14 for therapeutic application (A61P) and next are for formulation or process (C07C and C07D) − Figure 2.

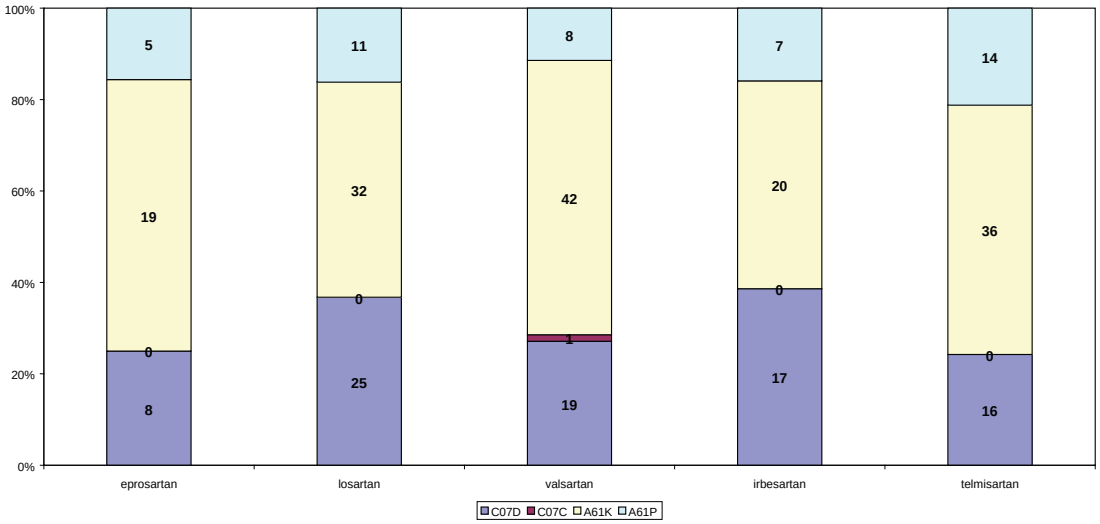

Fig. 2. Number of granted patents per IPC classes for the observed sartans

DISCUSSION AND LIMITATIONS

The discussion follows the answers of the study questions and additional comments are added for the differences.

Innovative and generic companies have very high patent activity. The time of the peak of the patent activity is different for both types of companies. Innovative companies became very active when the time for main patent expiration draws near. This result confirms the conclusions of other authors [25-27]. Such a patent policy leads to changes in the marketing authorization procedures, when a reference product is necessary for bioavailability analysis. It was permitted, in case the first original substance is lacking, to be used the so called European reference product that is any essentially similar product with a valid marketing authorization in Europe [33].

In the beginning of the observed period and for the older products patents for application (A61K) were usually granted to the generic companies. During the latest years after 2000 we observed that the generic companies started to follow the originators policy and to increase the researches and protection of different types of derivatives like salts, intermediates, polymorphs form, etc. of the main formulation near to patent expiration period. This is due to the solubility of the derivatives that is important for technology process of the dosage forms, or probably due to the results of the clinical trials for derivatives bioavailability. Thus the competition was transferred to therapeutic competitor that is exactly the situation observed in our study.

The highest number of patents granted for IPC class A61K (preparations for medical dental or toilet purposes) is probably due to the fact that this class is related to the possibility of the formulations to treat not only one symptom. Hypertension is a complex disease that is treated with a variety of medicines, as well as with combinations and all possible area of applications or combinations have been granted patents. For example, a patent for irbesartan is granted for all possible pharmaceutical compositions, observed for the studied medicines. Therapeutic activity (A61P) started to be protected since 1998 which could explain the small number of patents granted in this IPC class.

Per territory protection activity is similar with regard to the preference countries and follows the market dynamics and emergence. All products have been claimed for protection in the USA, EPO, India, China, Australia, Canada, and Japan. The countries out of WTO (Russia, South Africa etc.) became patent priority in the last 10 years.

The therapeutic competitors are more important than the generic ones within the sartans group. The first therapeutic alternatives appear earlier than the generic competitors. Thus the real life time of the main patent is therapeutically shortened and market monopoly is limited not on the basis of competition but due to the intensive work of the other innovators.

For some of the products, additional factors might play an important role in formulating the company patent protection policy. The permanent decrease in the number of patents for losartan could be due to the market reasons. Further studies are necessary to explore the effects of the market indicators on the patent protection policy.

The originality of this work is in the simultaneous comparison at a level of the two contemporary CV groups, and analysis of the influence of their patent protection at national policy level.

Specificity in the behavior of the originator companies is that they are more oriented towards protection of therapeutic combinations among the active substance and possible therapeutically compatible products, as well as towards the protection of new therapeutic use. The generic manufacturers are oriented towards the protection of new pharmaceutical formulations of the main active substance, as well as towards protecting the changes in processes of synthesis or manufacturing.

The similarities refer to the fact that both types of companies became more active in patent protection in a little while before the main patent expire.

CONCLUSIONS

Our study shows that a variety of factors are influencing the patent protection policy of pharmaceutical manufacturers, such as is the time of discovery, application of product, disease priority, technologies etc.

We found that therapeutic competition is more important than the generic ones for creating the patent profile of particular INN, which is in contrast with the beliefs that the patent protection policy affects mainly generic companies.

We also confirmed the results of similar studies that around the date of main patent expiration usually the activity of both originators and generic companies for granting new patents is increasing, probably due to the attempts to increase market monopoly of the product or to prevent other companies from market penetration.

REFERENCES

1. Magazzini, L., F. Pammolli et M. Riccaboni. Dynamic Competition in Pharmaceuticals: Patent Expiry, Generic Penetration, and Industry Structure. – The Eur. J. Health Econom., **2**, 2004, № 5, 175-182.
2. Fiona, M. Scott Morton, Entry Decisions in the Generic Pharmaceutical Industry. – In: NBER (National Bureau of Economic Research) Working Paper series, № 6190, Cambridge, **8**, 1997.
3. Fox, P. D. Prescription Drug Benefits: Cost Management Issues for Medicare. – Health care financing review, **25**, 2003-2004, № 2, 7-21.
4. Agreement on Trade-Related Aspects of Intellectual Property (1994)LT/UR/A-1C/IP/1art 1.
5. Cohen, J. C. et al. TRIPS, the Doha Declaration and increasing access to medicines: policy options for Ghana. – Globalisation and health, **1**, 2005, 17.
6. Jannuzzi, A. Vasconcellos Alexandre, de Souza Cristina. Cad. Saúde Pública, **24**, 2008, № 6, 1205-1218,.

7. C o r r e a , C. M. A guide to pharmaceutical patents, The South Centre, **1**, 2008, ISBN 92-9162-032-7.
8. S i b b a l d , B. Drug patent protection: How long is long enough? – CMAJ, **9**, 2001, № 1, 1331.
9. E s s , S. M., S. Schneeweiss et T. D. Szucs . European health care policies for controlling drug expenditure. – Pharmacoeconomics, **21**, 2003 № 2, 89-103.
10. M a n s l e y , E. C. et al. The utilization of medicines beyond patent expiration. – Forum for Health Economics and Policy, **11**, 2008, № 2, 11-18.
11. M o s s i a l o s , E., M. Mrazek et T. Walley. Regulating pharmaceuticals in Europe: striving for efficiency, equity and quality. European Observatory on Health Systems and Policies, Oxford University Press, 2004.
12. H o p k i n s , V. Analysis of international patent protection and global public health. http://www.princeton.edu/~jpia/pdf2006/JPIA%2006_1%20chapter%20copy%205.pdf (Accessed 15 July 2009).
13. C o r r e a , C. M. Implementing TRIPS in developing countries. Third World Economics 189. 1998, 16-31. http://www.twnside.org.sg/title/ment-cn.htm (accessed March 25, 2005).
14. C o r r e a , C. M. Integrating Public Health Concerns Into Patent Legislation In Developing Countries, 2000. http://www.southcentre.org/ publications/publichealth/publichealth.pdf (accessed March 24, 2005).
15. C o r r e a , C. M. Implications of the Doha Declaration on the TRIPS Agreement and Public Health. World Health Organization: Essential Drugs and Medicines Policy Series **12**, 2002a. http://www.who.int/medicines/areas/policy/WHO_EDM_PAR_2002.3.pdf (accessed March 25 2005).
16. C o r r e a , Carlos M. 2002b. Public and Intellectual Property Rights, Global Social Policy, **3**, 2002, 261-278.
17. C o r r e a , C. M. Recent International Developments In the Area of Intellectual Property Rights. Universidad de Buenos Aires ICTSD-UNCTAD Dialogue, 2nd Bellagio Series on Development and Intellectual Property, 2003. http://w w w .iprsonline.org/unctadictsd/bellagio/docs/Correa_Bellagio2.pdf (accessed March 28, 2005).
18. W o r l d Trade Organisation. Developing country group's paper. TRIPS: Council discussion on access to medicines. June 20. http//:www.wto.org/English/tratop_e/trips_e/paper_develop_w296_e.htm (accessed Fabruary 25, 2006)
19. D i r a c h , J. New safe medicines faster: A new concept for drug development. – EUFEPS. 27 Feb/ JDi; 1-5
20. F i o n a , M. Scott Morton, "Entry Decisions in the Generic Pharmaceutical Industry". – In: NBER (National Bureau of Economic Research) Working Paper series, № 6190, Cambridge, 1997, 8.
21. G a s c o n , F. et al. On macroeconomic characteristics of pharmecutical generics and the potential for manufacturing and consumption under fuzzy conditions. – Artificial Intell in med., **41**, 2007, 223-235.
22. W H O . Executive Board, 115 session. International Nonproprietary Names: revised procedure. Documents EB112/3 and EB112/2003/REC/1, summary record of the first meeting, section 4. http://apps.who.int/gb/ebwha/pdf_files/EB115/B115_11-en.pdf (Accessed 16 June 2009).
23. F y h r q u i s t , F. et O. Saijonmaa. Renin-angiotensin system revisited. – J. Intern. Med., **264**, 2008, № 3, 224-36.
24. R a i z a d a , M. K. et A. J. Ferreira. ACE2: a new target for cardiovascular disease therapeutics. – J. Cardiovasc Pharmacol., **50**, 2007, № 2, 112-119.
25. H o w a r d , L. Use of patents in drug lifecycle management. – J.Gener. Med., **4**, 2007, 230-236.
26. H o w a r d , L. Fluvastatin and atorvastatin: A comparison of patent protection (Part 1). – J. Gener. Med., **4**, 2007, 302-305.
27. H o w a r d , L. Fluvastatin and atorvastatin: A comparison of patent protection (Part 2). – J. Gener. Med., **5**, 2007, 85-90.

28. O r a n g e book: approved drug products with therapeutics equivalence evaluation. ttp://www.accessdata.fda.gov/ (Assess trough January 2006 – July 2009)
29. h t t p ://www.drugpatentwatch.com (Assess trough January 2006 – July 2009)
30. w w w .espacenet.com (Accessed trough January 2006 – July 2009)
31. R o s s i , S. et al. Australian Medicines Handbook 2006. Adelaide; 2006.
32. L e v y , B. I. How to explain the differences between renin angiotensin system modulators. – Am. J. Hypertens., **18**, 2005, 134S–141S.
33. C o u n c i l Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use. Official Journal L, 136, 30/4/2004, 34-57.

Address for correspondence:
Assoc. Prof. Assena Stoimenova, Ph. D., MPH
Faculty of Pharmacy
Department of Social Pharmacy and Pharmacoeconomics
Medical University – Sofia
2 Dunav str.,
1000 Sofia, Bulgaria
02/92 36 589
02/ 987 9874
0887 749 665
e-mail: assena_stoimenova@mail.bg