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Comparison of the Summary of Product Characteristics of Levocetirizine 5 mg According to Safety Criteria for Rational Drug Use

Ozaydin N[1*], Ozaydin AN[2]

[1]Pharmacology Department, School of Medicine, Okan University, Akfırat/Tuzla Istanbul, Turkey

[2]Department of Public Health, School of Medicine, Marmara University, Marmara Universitesi, Tıp Fakultesi, Halk Saglıgı AD, Basıbuyuk Kampusu, Maltepe Istanbul, Turkey

Mini Review

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***For Correspondence**

Fuat Nihat OZAYDIN, MD, Ph.D. in Pharmacology, Assistant Professor, Okan University, Pharmacology Department, School of Medicine, Akfırat/Tuzla Istanbul, Turkey, Tel: 0 (216) 677 16 47.

E-mail: fnozaydin@gmail.com

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ABSTRACT

Background: Anti-histamine drugs (AHDs) are employed for the treatment of allergic diseases. Second-generation AHDs such as levocetirizine is preferred today because they have fewer side effects than first-generation AHDs.

Methods: Content of the Summary of Product Characteristics (SPC) of levocetirizine (5 mg) approved by Health Authority of Turkey (HAT), US Food and Drug Administration (FDA) and European Medicines Agency (EMA) were compared to ascertain if there were differences according to safety criteria of rational drug use (RDU).

Results: The SPC of levocetirizine (5 mg) was prepared mainly by using information of the SPC from the EMA as a reference. However, some more vital safety features are present in the SPC from the FDA. Using the properties of the SPC from the FDA will be useful during preparation of the SPC for approval from the HAT with respect to the safety criterion of RDU.

INTRODUCTION

Pharmacologic properties of drugs are obtained from the Summary of Product Characteristics (SPC) [1]. The SPC is an extensive document detailing the indications, use, and the other basic information about a particular drug. It is prepared by the manufacturer and approved by Drug and Medical Device Institution of the Ministry of Health in Turkey, and its content cannot be changed without approval of the latter [2].

The Turkish Statistical Institute reported that allergy (allergic rhinitis, dermatitis, food allergy) was 3.1% and ranked thirteenth of all diseases diagnosed in Turkey in 2012 [3]. Anti-histamine drugs are one of the most prescribed drug groups for the treatment of adult allergic diseases [4,5]. First-generation anti-histamine agents have important side effects such as psychomotor disorders and cardiotoxicity. Hence, second-generation anti-histamine agents, which are considered to be more reliable with respect to side effects, are preferred [6,7]. Levocetirizine is example of second-generation anti-histamine agents [7] and are prescribed commonly in Turkey. In the present study, the SPC of levocetirizine (5 mg), which has been approved by the Health Authority of Turkey (HAT), US Food and Drug Administration (FDA), and European Medicines Agency (EMA), was compared to ascertain if there are differences according to the safety criteria of rational drug use (RDU). The latter refers to use of the most appropriate drug with respect to efficacy, safety, appropriateness and cost in the treatment of an illness [8].

METHODS

Contents of the SPC of levocetirizine (5 mg) were compared. The SPC of this second-generation anti-histamine agent was obtained from the Internet web pages of manufacturers originating from Turkey, the European Union, and USA. If this content could not be obtained from this Internet-based source, then the SPC approved by regulatory agencies was obtained from the Internet web pages of non-profit organizations.

The following features of SPC were compared and differences documented: posology and method of administration;

contraindications; warnings and precautions; interaction with other medicinal products and other form of interaction; fertility, pregnancy and lactation; effects on the ability to drive and use machines; undesirable effects; overdose; pharmacodynamics/ pharmacokinetics; and use in specific populations.

RESULTS

Similarities and differences in the SPC for levocetirizine (5 mg) from the HAT, EMA and FDA are explained under subheadings, as shown below.

Levocetirizine (5 mg)

Contents of the "interactions with other medicinal products and other forms of interaction", "fertility, pregnancy and lactation" "pharmacodynamics and pharmacokinetics" sections were similar, but the other parts of the SPC contained different information [9-11].

In the "dose and administration" section of the SPC from the FDA, it was advised to take levocetirizine (5 mg) in the evening, advice that was not provided in the SPC from the HAT or EMA.

Hypersensitivity to cetirizine was considered to be a contraindication in the SPC from the EMA and FDA, but this information was not present in the "contraindications" section of the SPC from the HAT. Moreover, levocetirizine was contraindicated for patients undergoing hemodialysis in the SPC from the FDA, but this information was not specified in the SPC from the EMA or HAT.

Effect of levocetirizine upon mental alertness was explained in the "special warnings and precautions" section of the SPC from the FDA, but was detailed in the "effects on the ability to drive and use machines" section of the SPC from the HAT and EMA. Levocetirizine use was not recommended in the SPC from the FDA. However, only "caution" during driving and other hazardous occupations necessitating mental alertness was advised in the SPC from the HAT and EMA.

Additional information was given in the "undesirable effects/adverse reactions" section of the SPC from the FDA: (a) as the dose of levocetirizine is increased, the incidence of somnolence increases; (b) movement disorders; (c) undesirable effects such as orofacial dyskinesia, severe hypotension, or cholestasis because levocetirizine is an active compound of cetirizine. This information was not provided in the SPC from the HAT or EMA.

In the "overdose" section, in addition to the information given in the SPC from the HAT and EMA, non-lethal doses for animals were given in the SPC from the FDA.

In the "use in special populations" section, levocetirizine doses were different for patients who had suffered renal failure. For example, in patients with mild renal impairment, 2.5 mg once-daily was recommended in the SPC from the FDA, but 5 mg once-daily was recommended in the SPC from the HAT and EMA.

Detailed information about the SPC from the HAT, EMA and FDA is given in **Table 1**.

DISCUSSION

The SPC of a certain drug is prepared according to rules set by the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH). The ICH brings together the regulatory authorities and pharmaceutical industry for drug registration. The mission of the ICH is to achieve greater harmonization worldwide to ensure that safe, effective and high-quality medicines are developed and registered [12]. The European Union, Japan, USA, Canada and Switzerland are regulatory members of this organization [13]. Turkey is not a member or observer of the ICH, but the drug-licensing procedures of Turkey are compatible with European Union Human Medicinal Products Regulations [14].

Although they are prepared according to ICH principles, the contents of some sections of the SPC of drug are different. Information that is absent in the SPC from the HAT and EMA may cause adverse events, as discussed below for levocetirizine.

Levocetirizine (5 mg)

No guidance for the time of levocetirizine administration was given in the SPC from the HAT and EMA. However, it was recommended that levocetirizine should be taken in the evening in the SPC from the FDA [9-11]. Moreover, avoidance of hazardous activities requiring complete mental alertness (e.g. driving, operating machinery) was highlighted in the "warnings" section of the SPC from the FDA. However, in the SPC from the HAT and EMA, patients were recommended only to consider their response to levocetirizine and to be cautious [9-11].

It is recommended that anti-histamine drugs with sedative properties should be taken at night because such properties continue to decrease through the following day. Additionally, use of such agents during hazardous activities is not recommended [7,15].

Levocetirizine is considered to be a sedative in the SPC from the FDA, but a non-sedative in the SPC from the HAT and EMA.

The "undesirable effects" section of the SPC from the HAT and EMA mentioned that the incidence of somnolence, fatigue and asthenia were more common using levocetirizine (5 mg) (8.1%) than placebo (3.1%) [9,10]. Moreover, somnolence and fatigue were

Table 1. Differences between Levocetirizine (5 mg) SPCs of HAT, EMA and FDA.

	SPCs of Turkey	SPCs of EMA	SPCs of FDA
Posology and method of administration	The daily recommended dose is 5mg	The daily recommended dose is 5 mg	The recommended dose of Levocetirizine is 5 mg once daily in the evening.
Contraindications	Hypersensitivity t to any other piperazine or to any of the other excipients. Patients with rare hereditary problems such as the Lapp lactase deficiency, galactose intolerance or glucose-galactose malabsorption should not take this medicine.	Hypersensitivity to the active substance, to cetirizine, to hydroxyzine, to any other piperazine or to any of the other excipients.	Patients with known hypersensitivity to levocetirizine or any of the ingredients of tablet, or to cetirizine. Patients undergoing hemodialysis
Special warnings and precautions			Avoid engaging in hazardous occupations requiring complete mental alertness such as driving or operating machinery when taking levocetirizine.
Effects on ability to drive and use machines	Nevertheless, some patients could experience somnolence, fatigue and asthenia under therapy with levocetirizine. Therefore, patients intending to drive, engage in potentially hazardous activities or operate machinery should take their response to the medicinal product into account.	Nevertheless, some patients could experience somnolence, fatigue and asthenia under therapy with levocetirizine. Therefore, patients intending to drive, engage in potentially hazardous activities or operate machinery should take their response to the medicinal product into account.	
Undesirable effects/Adverse reactions	The incidence of sedating adverse drug reactions such as somnolence, fatigue, and asthenia was altogether more common (8.1 %) under levocetirizine 5 mg than under placebo (3.1%).	The incidence of sedating adverse drug reactions such as somnolence, fatigue, and asthenia was altogether more common (8.1 %) under levocetirizine 5 mg than under placebo (3.1%).	In placebo-controlled trials of 1-6 weeks in duration, the most common adverse reactions were somnolence, nasopharyngitis, fatigue, dry mouth, and pharyngitis, and most were mild to moderate in intensity. Somnolence with levocetirizine showed dose ordering between tested doses of 2.5, 5 and 10 mg and was the most common adverse reaction leading to discontinuation (0.5%).
			Since levocetirizine is the principal pharmacologically active component of cetirizine, one should take into account the fact that the following adverse events could also potentially occur under treatment with levocetirizine: orofacial dyskinesia, severe hypotension, cholestasis, glomerulonephritis, still birth, tic, myoclonus, and extrapyramidal symptoms.
Overdose			The acute maximal non-lethal oral dose of levocetirizine was 240 mg/kg in mice (approximately 190 times the maximum recommended daily oral dose in adults, approximately 230 times the maximum recommended daily oral dose in children 6 to 11 years of age, and approximately 180 times the maximum recommended daily oral dose in children 6 months to 5 years of age on a mg/m2 basis). In rats the maximal non-lethal oral dose was 240 mg/kg (approximately 390 times the maximum recommended daily oral dose in adults, approximately 460 times the maximum recommended daily oral dose in children 6 to 11 years of age, and approximately 370 times the maximum recommended daily oral dose in children 6 months to 5 years of age on a mg/m2 basis).

Use in special populations	Dosing adjustments for patients with impaired renal function: Creatinine clearance (ml/min)≥ 80 (normal) : 1 tablet once a day Creatinine clearance (ml/min) 50-79 (mild) : 1 tablet once a day Creatinine clearance (ml/min) 30-49 (moderate) : 1 tablet once every 2 day Creatinine clearance (ml/min)<30 (severe) : : 1 tablet once every 3 day Creatinine clearance (ml/min)<10 (End-stage renal disease - Patients undergoing dialysis) : Contra-indicated	Dosing adjustments for patients with impaired renal function: Creatinine clearance (ml/min)≥ 80 (normal) : 1 tablet once a day Creatinine clearance (ml/min) 50-79 (mild) : 1 tablet once a day Creatinine clearance (ml/min) 30-49 (moderate) : 1 tablet once every 2 day Creatinine clearance (ml/min)<30 (severe) : : 1 tablet once every 3 day Creatinine clearance (ml/min)<10 (End-stage renal disease - Patients undergoing dialysis) : Contra-indicated	Dose Adjustment for Renal and Hepatic Impairment In adults and children 12 years of age and older with: Mild renal impairment (creatinine clearance [CLCR] = 50-80 mL/min): a dose of 2.5 mg once daily is recommended; Moderate renal impairment (CLCR = 30-50 mL/min): a dose of 2.5 mg once every other day is recommended; Severe renal impairment (CLCR = 10-30 mL/min): a dose of 2.5 mg twice weekly (administered once every 3-4 days) is recommended; End-stage renal disease patients (CLCR < 10 mL/min) and patients undergoing hemodialysis should not receive levocetirizine.

reported to be the most common side effects in the SPC from the FDA [14], thereby providing evidence of the sedative properties of levocetirizine.

Recently, second-generation anti-histamine drugs were divided into two subgroups: (i) drugs that result in mild sedation if the dose is doubled but sedation is not observed at a standard dose (e.g. cetirizine); (ii) drugs that do not result in sedation even if the dose is increased (e.g. fexofenadine) [16]. Increasing the dose by fourfold or more for the treatment for urticaria makes this new classification important. The SPC from the FDA stated that somnolence with levocetirizine was dose-dependent at 2.5, 5 and 10 mg and was the most common adverse reaction leading to discontinuation of use. However, such data were not given in the SPC from the HAT or EMA [9-11].

In a new clinical study, levocetirizine (5 mg) crossed the blood–brain barrier and was bound to brain H1 receptors at ≤ 11%. This binding rate did not cause sedation but “true” non-sedating anti-histamine agents should not occupy H1 receptors in the brain. The binding rate to H1 receptors in the brain using higher doses of levocetirizine is not known [17].

As well as fatal occupational accidents, traffic accidents have a high incidence and are the ninth leading cause of death in Turkey [18]. Therefore, differences in information on sedative/non-sedative agents between SPCs are very important because they protect healthcare providers against medico legal risks [19].

The main strength of our study was that we were able to compare the SPCs of the same commercial product and/or the same manufacturer. The main limitation of our study was that the Internet website of the HAT required a password and only institutional applications from pharmaceutical companies were accepted. Therefore, the SPC could not be examined through the Internet webpage of the Drug and Medical Device Institution of the Ministry of Health [20].

CONCLUSION

The SPC of levocetirizine (5 mg) was prepared mainly by using information of the SPC from the EMA as a reference. However, some more vital safety features are present in the SPC from the FDA. Using the properties of the SPC from the FDA will be useful during preparation of the SPC for approval from the HAT with respect to the safety criterion of RDU and they protect healthcare providers against medicolegal risks.

REFERENCES

1. Filiz Başaran N, Akıcı A. Aspects of physicians' attitudes towards the rational use of drugs at a training and research hospital: A survey study. Eur J Clin Pharmacol. 2013;69:1581-1587.
2. Notification to applicants. Short Product Information guide. 2016.
3. Turkish Statistical Institute. Ankara: Turkey Health Survey, Table 4: Distribution of disease/health problems diagnosed by physician in the age group of 15 years and over by gender and residence. 2016.
4. Gholam-Hossein S, et al. Prescribing quality in medical specialists in Isfahan, Iran. Iran J Pharm Res. 2013;12:235-241.
5. Gopalakrishnan S, et al. Assessment of prescribing practices among urban and rural general practitioners in Tamil Nadu. Indian J Pharmacol. 2013;45:252-257.
6. Greaves MW. Antihistamines in dermatology. Skin Pharmacol Physiol. 2005;18:220-229.

7. Kavosh ER, Khan DA. Second-generation H1-antihistamines in chronic urticaria. An evidence-based review. Am J Clin Dermatol. 2011;12:361-376.
8. Oktay S. General principles of rational drug use. Turk J Geriatr. 2006;15-18.
9. http://www.medicines.org.uk/emc/medicine/7739
10. http://www.chiesi.com.tr/Contents/Product/3678203d-9c9f-4c68-9633-cbcbeb2f1c60.pdf
11. http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022064s028_022157s012lbl.pdf
12. ICH. Harmonisation for beter health. Welcome to the official website. 2016.
13. ICH. Harmonisation for beter health. ICH announces organisational changes as it marks 25 years of successful harmonisation. 2016.
14. Gazete R. Ruhsatlandırılmış veya Ruhsatlandırma Başvurusu Yapılmış Beşeri Tıbbi Ürünlerdeki Değişikliklere Dair Yönetmenlik. 2016.
15. Nicholson AN. Antihistamines and sedation. Lancet. 1983;2:211-212.
16. Hiroyuki K, et al. Effects of single therapeutic doses of promethazine, fexofenadine and olopatadine on psychomotor function and histamine-induced wheal- and flare-responses: A randomized double-blind, placebo-controlled study in healthy volunteers. Arch Dermatol Res. 2012;304:263–272.
17. Hiraoka K, et al. Brain histamine H1 receptor occupancy measured by PET after oral administration of levocetirizine, a non-sedating antihistamine. Expert Opin Drug Saf. 2015;14:199-206.
18. https://sbu.saglik.gov.tr/Ekutuphane/Yayin/166
19. Sewal RK, et al. Forensic pharmacovigilance: Newer dimension of pharmacovigilance. J Forensic Leg Med. 2015;34:113-118.
20. http://www.titck.gov.tr/KubKt/Login