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The impact of chiral switch on drug labeling in Turkey: indication, posology, and adverse effects

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ABSTRACT

Objective: Chiral switch, which involves replacing racemic drugs to market them as pure enantiomers, is presumed to improve efficacy and safety. Data on how chiral switch-related changes are represented in summary of product characteristics (SmPC) is scarce. We aimed to compare the indication, posology, and safety expressions in SmPCs of racemates and their pure enantiomers.

Materials and Methods: We examined SmPCs of nine drug pairs (racemate/pure enantiomer) that underwent chiral switching among top 100 utilized active substances throughout Turkey. We evaluated the expressions in "indications", "posology", and "adverse effects" (AE) subheadings. Daily doses were examined based on "Defined Daily Dose" (DDD) metric.

Results: We detected indication differences in four drug pairs, including absence of "peptic ulcer" in dexlansoprazole and "prevention of depression relapses" in escitalopram. DDDs of pure enantiomers decreased in most of the pairs. Recommended daily doses of esomeprazole and dexibuprofen per DDD were lower than their racemates. Cautions about use in renal and/or hepatic insufficiency varied in three pairs. AE expressions differed in seven drug pairs, mainly citalopram/escitalopram.

Conclusion: This study demonstrated few indication differences in SmPCs of the drug pairs frequently used in Turkey and underwent chiral switching. However, dose reductions and distinctions in safety expressions were remarkable.

Keywords: Chirality, Chiral switch, Pure enantiomer, Racemate, Summary of product characteristics, Health policy

1. INTRODUCTION

Chirality, an important geometric property of chemical compounds, is simply defined as the non-overlapping of the molecule with its mirror image. This feature is also frequently encountered in drug molecules [1-4]. It is known that more than half of the conventional medications with small-molecule structure in the current pharmaceutical market contain at least one asymmetric center. The share of pure enantiomers in newly authorized medications has progressively grown over the years [5,6]. Among small-molecule pharmaceuticals available on the market, pure enantiomers were triple the racemates as reported in our recently published work [7].

Although, chiral compounds are common in body components, it is well known that many critical physiological processes are stereoselective and utilize just one potential enantiomer [1]. This geometric characteristic has been shown to cause substantial pharmacokinetic and pharmacodynamic variations for drug molecules [8]. The variations in efficacy and safety which pure enantiomers might exhibit have sparked controversy regarding whether these compounds should be studied as distinct drug candidates [1,9,10]. The replacement of the already approved racemate with the single enantiomer form on the market is referred to as chiral switch. The goals of this process include more accurate pharmacodynamic profile, broader therapeutic index, improved safety profile, reduced risk of undesired drug interactions, rapid onset of effect, and dosage reduction [1,2]. Most authorities, however, do not require that the pure enantiomer be compared to the racemate product during the medication approval procedure. Furthermore, there is a scarcity of data on the efficacy and safety variations attributed to chiral switch in labeling information of the drugs, creating a knowledge gap in this context [1,11,12]. Summaries of product characteristics (SmPCs) are official sources of information about

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the drug product for healthcare professionals [13]. We aimed to compare the SmPCs of the products that have undergone chiral switch and marketed as racemate and pure enantiomer in Turkey in terms of indication, posology, and safety.

2. MATERIALS and METHODS

In this study, we evaluated SmPCs of drugs that have undergone chiral switch process. While determining the active substances, the chirality status of the 100 most used drugs in Turkey were examined. For this purpose, we used outpatient drug sales data of 2021 obtained from the Turkey branch of IQVIA (formerly Quintiles and IMS Health), which is a global provider of advanced analytics to the healthcare industry. IQVIA provides complete and statistically validated data without any projection, measuring the number of packs at the wholesale distribution level [14]. Among top 100 active substances marketed as non-combination preparations, we identified seven racemates (ibuprofen, lansoprazole, salbutamol, cetirizine, rabeprazole, ketoprofen, amlodipine) and three pure enantiomers (dexketoprofen, esomeprazole, escitalopram) that underwent chiral switch to include in the study. We also added the racemate/pure enantiomer counterparts of those identified active substances. As both the racemate and the pure enantiomer of the ketoprofen/dexketoprofen pair were listed in top 100 drugs, we achieved a total of 18 drugs/nine drug pairs to include in the study. We selected the SmPCs of the identified drugs from the database of Turkish Medicines and Medical Devices Agency [15]. The SmPC of a particular drug brand was eligible if it (i) was a non-combination medicinal product; (ii) belonged to an oral formulation (to minimize comparability issues implied by possible expression discrepancies, given the majority of marketed medications are in oral form), (iii) was preferably an original brand. If an original brand was available, the one that contains the strength of drug dose recommended by the World Health Organization's (WHO) defined daily dose (DDD) metric was selected. If an original brand was not available, we selected the brand with the latest approval date among the ones that had the same formulation and DDD in the database (Table I). We examined the similarities and differences of the expressions in the SmPCs of the chiral-switched racemate and pure enantiomer pairs under "therapeutic indications", "posology" and "adverse effects (AE)" headings. We analyzed all indications under the heading of "therapeutic indications" and only those AEs categorized as "very common" and "common". Subsequently, we classified the shared and different parameters for each heading. In posology analyses, we evaluated the similarities and differences by comparing the daily recommended dose, daily maximum dose, and the need for dose adjustments in renal failure and liver failure for drug pairs based on DDD [16]. The study does not contain patient data and does not require ethics committee approval.

3. RESULTS

Indications

Among the three PPI pairs, we found no difference between rabeprazole and dexrabeprazole in terms of indications. Lansoprazole was indicated in duodenal, gastric, and non-steroidal anti-inflammatory drug (NSAID)-associated ulcers, *H. pylori* eradication, and Zollinger-Ellison syndrome, whereas its pure enantiomer, dexlansoprazole, was not. In omeprazole/esomeprazole pair, the latter was additionally indicated for short-term maintenance of hemostasis after parenteral PPI treatment. For the differences in selective serotonin reuptake inhibitor (SSRI) pair, citalopram was additionally indicated in prevention of relapses/recurrences of depression whereas escitalopram was distinctly indicated in social and generalized anxiety disorders. In NSAID pairs, ibuprofen was additionally indicated in symptomatic treatment of certain rheumatoid conditions while therapeutic indication of dexibuprofen specified dental pain distinct from its racemate. We found no difference for the drug pairs of ketoprofen/dexketoprofen, cetirizine/levocetirizine, salbutamol/levosalbutamol, and amlodipine/S-amlodipine (Table II).

Posology

We determined that DDDs of pure enantiomers was lower in four of the six drug pairs for which DDD information was available. Among the remaining, esomeprazole had higher DDD (30 mg) than that of omeprazole (20 mg) while dexlansoprazole/lansoprazole pair had no difference in DDD. In terms of recommended daily doses in the SmPCs, esomeprazole and dexibuprofen had lower DDDs compared to that of their racemates. The maximum daily doses of dexibuprofen, dexketoprofen, levosalbutamol, and S-amlodipine were lower than that of their racemates (Table III).

The expressions about dose adjustments for renal failure overall showed consistency except for omeprazole/esomeprazole and ibuprofen/dexibuprofen pairs. While omeprazole did not require dose adjustment, its pure enantiomer had a warning to use carefully in severe failure. Ibuprofen was indicated to use as lowest possible dose in renal failure where dexibuprofen was not recommended if the condition was severe. The major difference in terms of hepatic dysfunction was observed for the lansoprazole/dexlansoprazole pair where the racemate required halving of the dose in severe liver failure for which the pure enantiomer was recommended against use (Table III).

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Table I. *Distribution of racemate and pure enantiomer drug pairs undergoing chiral switch.*

Racemate		Pure enantiomer	
Active substance	**Drug brand**	**Active substance**	**Drug brand**
Omeprazole	Demeprazol® 20 mg capsules*	Esomeprazole	Nexium® 20 mg enteric-coated pellet tablets
Lansoprazole	Lansoprol® 30 mg enteric-coated micropellet capsules*	Dexlansoprazole	Dexapol® 30 mg enteric-coated micropill-containing capsules*
Rabeprazole	Pariet® 20 mg enteric tablets	Dexrabeprazole	Rabby-D® 10 mg enteric-coated tablets*
Ibuprofen	Brufen® 600 mg film-coated tablets	Dexibuprofen	Tradil® fort 400 mg film tablets
Ketoprofen	Bi-Profenid® 100 mg ER tablets	Dexketoprofen	Arveles® 25 mg film-coated tablets
Citalopram	Cipram® 20 mg film-coated tablets	Escitalopram	Cipralex® 10 mg film-coated tablets
Cetirizine	Zyrtec® 10 mg film-coated tablets	Levocetirizine	Xyzal® 5 mg film-coated tablets
Salbutamol	Ventolin® 100 mcg pressurized inhalation suspension	Levosalbutamol	Inhawell® 100 capsule-containing powder for inhalation*
Amlodipine	Norvasc® 5 mg tablets	S-amlodipine	S-Nor® 2.5 mg tablets*

**Generic brand, ER, extended-release*

Table II. *Comparison of chiral active substance pairs in terms of licensed indications.*

Drugs	Mutual indications	Differences
Omeprazole	– Reflux esophagitis (treatment and prophylaxis) – Symptomatic GERD – Zollinger-Ellison syndrome – H. pylori eradication – NSAID-related peptic ulcer (treatment and prophylaxis) – Peptic ulcer prophylaxis	– Peptic ulcer treatment
Esomeprazole		– Short-term maintenance of hemostasis in peptic ulcers
Lansoprazole	– Reflux esophagitis treatment – Reflux esophagitis prophylaxis – Symptomatic GERD	– Duodenal ulcer – Gastric ulcer – *H. pylori* eradication – NSAID associated ulcer – Zollinger-Ellison syndrome
Dexlansoprazole		
Rabeprazole	– Active duodenal ulcer – Active benign gastric ulcer – GERD treatment – GERD maintenance therapy – Symptomatic GERD – Zollinger-Ellison syndrome – H. pylori eradication in peptic ulcer patients	
Dexrabeprazole		
Ibuprofen	– Osteoarthritis symptoms – Dysmenorrhea – (Acute±) Musculoskeletal pain	– RA symptoms – Ankylosing spondylitis symptoms – Acute gouty arthritis – Postoperative pain
Dexibuprofen		– Dental pain
Ketoprofen	– Osteoarthritis symptoms – RA symptoms – Ankylosing spondylitis symptoms – Acute gouty arthritis – Acute musculoskeletal pain – Postoperative pain – Dysmenorrhea	
Dexketoprofen		
Citalopram	– Depression treatment – Panic disorder – Obsessive compulsive disorder	– Prevention of depression relapses/recurrences
Escitalopram		– Social anxiety disorder – Generalized anxiety disorder
Cetirizine	– Symptoms of allergic rhinitis – Urticaria symptoms	
Levocetirizine		
Salbutamol	– Asthma symptoms – COPD symptoms	
Levosalbutamol		
Amlodipine	– Essential HT – Chronic stable angina – Vasospastic angina	
S-amlodipine		

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Table III. *Comparison of DDD and the posology characteristics of chiral drug pairs declared in SmPCs.*

Drugs	Daily recommended dose	DDD	Maximum daily dose	Dose in renal impairment	Dose in hepatic impairment
Omeprazole	1 x DDD	20 mg (GERD)	N/A	Dose adjustment is not required	10-20 mg daily
Esomeprazole	(2/3) x DDD*	30 mg[a] (GERD)	N/A	Mild to moderate: No dosage recommendation Severe: Should be cautious	Mild to moderate: No dosage recommendation Severe: 20 mg maximum
Lansoprazole	1 x DDD	30 mg (GERD)	N/A	Dose adjustment is not required	Moderate to severe: Half the daily dose
Dexlansoprazole	1 x DDD	30 mg[c] (GERD)	N/A	Dose adjustment is not required	Mild: No dosage adjustment required Moderate: Maximum of 30 mg daily Severe: Use not recommended
Rabeprazole	1 x DDD	20 mg (GERD)	N/A	Dose adjustment is not required	Dose adjustment is not required
Dexrabeprazole	10 mg (GERD)	(N/A)[d]	N/A	Dose adjustment is not required	Dose adjustment is not required
Ibuprofen	1 to (3/2) x DDD	1200 mg (rheumatoid arthritis)	2 x DDD	Minimum possible dose	Minimum possible dose
Dexibuprofen	3/4 x DDD*	800 mg[b] (rheumatoid arthritis)	3/2 x DDD[#]	Mild to moderate: Reduced initial dose (not specifically specified) Severe: Use not recommended	Mild to moderate: Reduced initial dose (not specifically specified) Severe: Use not recommended
Ketoprofen	(2/3) to (4/3) x DDD	150 mg (rheumatoid arthritis)	4/3 x DDD	Reduced initial dose (not specified) Severe: Contraindicated	Minimum effective daily dose Severe: Contraindicated
Dexketoprofen	(2/3) to 1 x DDD	75 mg[b] (rheumatoid arthritis)	1 x DDD[#]	Mild: 50 mg daily Moderate to severe: Use is not recommended	Mild: 50 mg daily Moderate to severe: Use is not recommended
Citalopram	1 x DDD	20 mg (depression)	2 x DDD	Mild to moderate: No dosage adjustment required Severe: Should be cautious	Mild to moderate: Initial 10 mg, maximum 20 mg Severe: Caution, slow titration
Escitalopram	1 x DDD	10 mg[b] (depression)	2 x DDD	Mild to moderate: No dosage adjustment required Severe: Should be cautious	Mild to moderate: Initial 5 mg, maximum 10 mg Severe: Caution, slow titration
Cetirizine	1 x DDD	10 mg	N/A	Mild: No dosage adjustment required Moderate: 5 mg daily Severe: 5 mg every other day ESRD/dialysis: Contraindicated	Dose adjustment is not required
Levocetirizine	1 x DDD	5 mg[b]	N/A	Mild: No dosage adjustment required Moderate: 5 mg every other day Severe: 5 mg every three days ESRD/dialysis: Contraindicated	Dose adjustment is not required
Salbutamol	(1/8) to (1/2) x DDD	0.8 mg inh. aerosol/ powder (asthma)	1 x DDD (800 mcg)	No data	No data
Levosalbutamol	100 mcg every 4-6 hours	(N/A)[d]	100 mcg (1 inh. dose)[#] 6 times a day	Should be cautious	Dose adjustment is not required
Amlodipine	1 x DDD	5 mg (HT)	2 x DDD	Dose adjustment is not required	Minimum initial dose, slow titration
S-amlodipine	2.5 mg (initial dose)	(N/A)[d]	5 mg[#]	Dose adjustment is not required	Minimum initial dose, slow titration

**Different from the Defined Daily Dose (DDD) posology of the World Health Organization, a: those whose DDD is increased compared to its racemate, b: those whose DDD is reduced compared to its racemate, c: those whose DDD is unchanged compared to its racemate, d: Those who do not have DDD but whose daily dose is reduced compared to their racemate in the SmPC declaration, #: represents those with reduced maximum daily dose compared to its racemate.*

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Table IV. *Comparison of chiral drug pairs in terms of very common and common adverse effects.*

Drugs	Mutual adverse effects	Differences
Omeprazole	-Headache	-
Esomeprazole	-Abdominal pain, constipation, diarrhea, bloating, vomiting, nausea, benign fundic gland polyps	-
Lansoprazole	-Headache -Nausea, diarrhea, abdominal pain, constipation, flatulence	-Dizziness -Vomiting -Dry mouth/throat -Increased liver enzymes -Urticaria, itching, redness -Fatigue
Dexlansoprazole		-Fundic gland polyps
Rabeprazole	-Infection -Insomnia -Headache, dizziness -Cough, pharyngitis, rhinitis -Diarrhea, vomiting, nausea, abdominal pain, constipation, flatulence -Non-specific pain, back pain -Asthenia, flu-like illness	-Fundic gland polyps
Dexrabeprazole		-
Ibuprofen	-Nausea, vomiting, abdominal pain -Rash -Headache, dizziness -Fatigue	-Dyspepsia, diarrhea, flatulence, constipation, melena, hematemesis, GI bleeding
Dexibuprofen		**-Dyspepsia, diarrhea** -Somnolence, vertigo
Ketoprofen	-Nausea, vomiting, dyspepsia, abdominal pain	-
Dexketoprofen		-Diarrhea
Citalopram	-Decreased appetite -Anxiety, abnormal dreams, female anorgasmia, decreased libido, agitation -Tremor, paresthesia -Yawning -Nausea -Diarrhea, constipation, vomiting -Increased sweating -Myalgia, arthralgia -Impotence, ejaculation disorder	**-Insomnia, somnolence** **-Headache** **-Dry mouth** -Weight reduction -Dizziness, attention disorder, migraine, amnesia -Tinnitus -Palpitations -Rhinitis -Dyspepsia, abdominal pain, bloating, excessive salivation -Itching -Asthenia -Fatigue
Escitalopram		-Increased appetite, weight gain -Irritability, confusion, apathy -Headache -Insomnia, somnolence, dizziness -Sinusitis -Dry mouth -Weakness, fever
Cetirizine	-Headache -Somnolence -Dry mouth -Weakness	-Nausea -Pharyngitis -Dizziness
Levocetirizine		-
Salbutamol		-Tremor, headache -Tachycardia
Levosalbutamol		-Dizziness -Pain -Asthma, pharyngitis, rhinitis
Amlodipine	**-Somnolence, dizziness, headache** **-Edema** -Visual impairment, diplopia -Palpitations -Facial flushing -Dyspnea -Abdominal pain, nausea, dyspepsia, change in bowel movements -Ankle swelling, muscle cramps -Fatigue, asthenia	-
S-amlodipine		

Very common adverse reactions are denoted by bold font.

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Adverse effects

In PPI pairs, we identified the major AE difference between lansoprazole/dexlansoprazole was the frequent prevalence of "dizziness, vomiting, dry mouth/throat, increased liver enzymes, urticaria/itching/redness, and fatigue" in lansoprazole compared to its enantiomer which distinctly exhibited "fundic gland polyps" as frequent AEs. Among substantial differences in gastrointestinal and central nervous system AEs between the SSRI pair, insomnia/somnolence, headache, and dry mouth was listed as "very frequent" for citalopram and as "frequent" for escitalopram. In addition, these drugs also differed in terms of their frequent weight-related AEs that citalopram was associated with weight loss compared to the association of escitalopram with weight gain (Table IV).

In NSAID pairs, ibuprofen indicated dyspepsia and diarrhea as frequent AEs, which were listed as very frequent for dexibuprofen. On the other hand, this pure enantiomer lacked flatulence, constipation, melena, hematemesis, and gastrointestinal bleeding, AEs which were categorized as frequent for ibuprofen. The antihistamine racemate cetirizine showed nausea, pharyngitis, and dizziness as frequent AEs, which were not listed as frequent or very frequent by its pure enantiomer, levocetirizine. Similarly, the frequent AEs of tremor, headache and tachycardia of the salbutamol was not observed in the frequent/very frequent AE category of its pure enantiomer (Table IV).

4. DISCUSSION

Although, health authorities have defined criteria for the official drug documents, especially SmPCs, it is known that problems can be encountered regarding their standardization and compliance with the current literature [17,18]. Moreover, the reflection of the data on the efficacy and safety differences resulting from the chiral switch to drug labels is limited [1,19]. The up-to-dateness of these documents, approved by health authorities, is important to achieve all global health goals positioned within the framework of "good health and well-being" [19,20]. Our study focused on the prominent differences in the SmPCs of the preparations that have undergone chiral switch and are available in both the racemate and pure enantiomer form in the pharmaceutical market.

Since, the pure enantiomer of three of the four racemates available in Turkey is also available in the market, PPIs are among the drug groups that have undergone chiral switch substantially. As a result of the chiral switch, esomeprazole, dexrabeprazole and dexlansoprazole were included in the global pharmaceutical market [21-23]. The advantages expected to emerge with the chiral switch of PPIs include increased bioavailability, prolonged intragastric pH control, and less inter-individual variability in drug metabolism [22,24]. On the other hand, it is known that the active substances in this group are similar in terms of clinical efficacy and therapeutic areas [25]. Six of the seven indication differences between the PPI pairs examined in our study were related to peptic ulcer treatment. Although, there are studies showing that the pure enantiomer of the lansoprazole/dexlansoprazole pair, in which the majority of these differences was observed, may be effective in the treatment of *H. pylori*-associated peptic ulcer [26,27], it was noteworthy that dexlansoprazole is not indicated for duodenal, gastric and NSAID-related ulcers. Besides, the additional indication for the short-term maintenance of hemostasis in esomeprazole compared to omeprazole may be related to the fact that this PPI pair provides similar intragastric pH control, but the pure enantiomer provides >24 hours of intragastric pH stabilization in more patients compared to the racemate [21]. In a meta-analysis including randomized trials of the lansoprazole and dexlansoprazole where almost all AE differences were observed, it was reported that these drugs were similar in terms of safety endpoints [12,28].

One of the potential advantages of chiral switch is the limitation of drug doses to which the patient is exposed [29]. In the conversion of drugs in which one of the two enantiomers in the structure of the racemate provides the therapeutic effect and the other is inert, the therapeutically effective enantiomer is purified and the dose of the drug to which the patient will be exposed can be reduced accordingly [30]. Except for esomeprazole and dexlansoprazole, the recommended daily dose of pure enantiomers was lower than their racemates in all of the pairs examined in the study, suggesting that this target of chiral switch can often be achieved. While, the recommended daily doses of the racemate and the pure enantiomer were the same in the two PPI pairs in which no dose reduction was observed, it was noteworthy that the DDD value of esomeprazole was higher than that of omeprazole. Of the 17 studies in a meta-analysis comparing esomeprazole to its racemate, nine received higher doses of esomeprazole than omeprazole. Based on the results of 10 of these 17 studies, the safety profile of the two drugs was reported to be generally similar [31]. The fact that studies provide evidence in favor of the safety of high doses of esomeprazole may have paved the way for the widespread use of the drug at these doses. However, the direct relationship of this situation with chirality is doubtful. Another pair of PPIs, lansoprazole and dexlansoprazole, were similar in terms of both recommended daily dose and DDD values. This situation may be related to the fact that dexlansoprazole is presented in a dual-delayed release (DDR) formulation rather than stemming from chiral switch. In the DDR formulation, the drug consists of a mixture of two different types of granules, one release in the proximal duodenum and the other in the distal small intestine. It is stated that the drugs in this formulation require a higher daily dosage administration as they release for a longer period of time than conventional delayed-release PPIs [31]. This may suggest that the posology differences observed in both drug pairs are unlikely to be chirality related.

Ibuprofen and ketoprofen, which are arylpropionic acid derivatives, are among the racemic NSAIDs that undergo chiral switch. The S-enantiomers of these drugs are mainly responsible for the anti-inflammatory effect and have been introduced to the market after chiral switch. This switch is aimed at faster onset of action and less individual variability in drug response [1,32]. On

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the other hand, the fact that the R-enantiomers of these drugs are converted to S-enantiomers as a result of chiral inversion in the body (approximately 60% in ibuprofen, ≤15% in ketoprofen) has led to debates that the biological effect difference between drugs is limited [1,30,32]. Indication and AE differences in NSAIDs were mainly observed in the ibuprofen/dexibuprofen pair. Only ibuprofen was approved for the symptomatic treatment of certain rheumatic disorders, but dexibuprofen was not. However, in a review of eight clinical studies and three observational studies, dexibuprofen was reported to be similarly effective with its racemate in these conditions [33]. In terms of safety, the frequencies of "dyspepsia" and "diarrhea" were stated more frequently in dexibuprofen, but the number of gastrointestinal AE expressions were higher in ibuprofen. In fact, a study conducted with osteoarthritis patients in Austria, reported that gastrointestinal complaints were >2 times higher in ibuprofen compared to the enantiomer [34]. On the other hand, a Korean study conducted in children reported no safety difference between the two drugs [35]. This suggests that the differences reflected in the safety profile may be related to the indication and target patient population. Indication and AE expressions of ketoprofen/dexketoprofen, the other NSAID pair studied, were largely similar. In a systematic review evaluating 24 studies, it was reported that these two drugs have similar efficacy and safety profiles [36].

Unlike the ones in citalopram, the SmPC of escitalopram showed indication statements about anxiety disorders. It has been suggested that the S-enantiomer (escitalopram) of citalopram is the part that is effective in the treatment of anxiety disorders [37]. Escitalopram was reported to be superior to its racemate in terms of efficacy in seven studies comparing citalopram [38]. The fact that the pure enantiomer drug has indications related to anxiety, unlike its racemate, may be associated with this evidence. However, although it is not among the indications of citalopram, it has been reported that this chiral mixture has benefits in anxiety disorders and included in the guidelines, albeit trailing behind escitalopram [39,40]. As in this case, it might be suggested that physicians, while prescribing drugs, do not necessarily adhere to the approved indications and may use some drugs off-label for conditions where their efficacy has been established. We observed substantial AE differences statements for the citalopram/escitalopram pair, especially regarding the central nervous and gastrointestinal system. Theoretically, separation of escitalopram from its R-enantiomer is expected to positively affect the safety profile of the drug, but it is stated that the frequency of AEs and tolerability of drugs are similar in the majority of clinical studies in the literature [1,12,41]. It is unclear if AE declaration differences as those seen in this drug pair are the product of statistical evaluation of clinical trial-based safety data or post-marketing routine pharmacovigilance data. Considering that documentation errors may have contributed to this situation, our findings may imply that this problem, which complicates standardizing and homogenizing the label expressions, merits further examination.

The fact that levocetirizine has up to 30 times greater affinity for H1 receptors than dextrocetirizine and exhibits approximately 10 times more potency is among the reasons for the chiral switch of cetirizine [1,42]. On the other hand, the superiority of levocetirizine to cetirizine in terms of effectiveness is controversial. The efficacy of the drugs was compared in three studies evaluated in a meta-analysis, and only one study reported that levocetirizine was more effective than its racemate [12]. As would be expected, this suggest overlapping of the indication statements in the respective SmPCs. In terms of safety, the expressions "nausea", "pharyngitis" and "dizziness" in the SmPC of cetirizine were not found in levocetirizine. However, the same meta-analysis, reported no superiority of either drug to each other in terms of safety [12]. The discrepancies between the data sourced for SmPCs and the results of the limited studies in the literature suggest that more studies are needed to compare the two drugs in terms of efficacy and safety. Similar to that in cetirizine/levocetirizine, the indication expressions in the labels of the salbutamol/levosalbutamol pair were similar, while "tremor and headache" and "tachycardia" AEs found in salbutamol were not present for levosalbutamol. Increased potency and reduced airway hyperreactivity have been pointed out as potential advantages of the chiral switch seen in this drug pair [1,41]. As a result of the two studies comparing the drugs, it was reported that there was no significant difference between the racemate and the pure enantiomer in terms of AEs such as tremor and headache [43].

In our study, edema and ankle swelling were expressed in both amlodipine and S-amlodipine SmPCs, with similar frequencies for both drugs. A meta-analysis reported that peripheral edema of the lower extremities was less common in S-amlodipine users compared to racemic amlodipine users, but the evidence was weak in quality [44]. However, a more recent randomized controlled trial reported that S-amlodipine used at half the dose of the racemate caused less leg edema [45,46]. Furthermore, it was reported that nearly 90% of patients who had edema while taking racemic amlodipine had their symptoms resolved after switching to the S-enantiomer form [46]. This suggests that there may be problems with updating drug labels or failing to respond soon enough in the light of recently added studies to the literature.

Our study has some limitations. First of all, the chirality characteristics of all drugs available in the market could not be examined. This limitation was tried to be mitigated as much as possible by examining the chirality characteristics of the mostly consumed drugs in Turkey. However, although there are similarities in some groups, it should be kept in mind when evaluating the results of this study that the most consumed drugs in Turkey may not necessarily exhibit parallel trends with the rest of the world. Another limitation of the study can be considered as not examining the sections other than indications, posology, and AEs in the SmPCs of drug pairs. The lack of DDD values for some pure enantiomers can be considered as a limitation, especially for posology-based findings. Given the possibility of variances depending on SmPC documentation of the preparations of each active ingredient, the fact that all the marketed preparations of the drug pairs examined in the study could not be assessed is another limitation. Nevertheless,

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considering that the drug labels should provide standard expressions between the preparations of the same active ingredient, it highlights the need for the parties to re-examine the substantial discrepancies discovered in the SmPCs for all relevant preparations.

Conclusion

We shed light on the differences observed in chiral switch products and the reflections of changes in drug labels. Accordingly, we observed a few differences in indications, several dosage reductions, and substantial differences in AE profile amongst the drug pairs. The limited clinical efficacy and safety benefits of the pure enantiomer after chiral switch suggest that a more selective approach should be followed before its use. Generally, reflections of chiral switch to recommended doses have been observed. On the other hand, although chiral drug pairs are similar to each other in terms of indication and AE according to the literature, it seems that various differences can be encountered in SmPCs due to both documentation problems and lack of up-to-dateness. The potential advantages of chiral switch in terms of efficacy, safety, and suitability are likely to be retained in the future. It is crucial to ensure uniformity while the data on chiral switch are reflected in drug-related official documents. Our study is expected to contribute to the relevant stakeholders in terms of developing SmPCs to provide accurate and up-to-date information. In this context, updated SmPCs will be expected to contribute more to the maintenance of good health and well-being.

Compliance with Ethical Standards

Ethics Committee: The study does not contain patient data and does not require ethics committee approval.

Conflict of Interest: The authors declare that they have no conflicts of interest.

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