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# OFF-LABEL AND UNLICENSED ENDOCRINOLOGY MEDICINE USE IN TURKEY: A RETROSPECTIVE ANALYSIS OF COMPUTER RECORDS IN THE TURKISH MINISTRY OF HEALTH

## Original Article

# TÜRKİYE`DE ENDİKASYON DIŞI VE LİSANSSIZ ENDOKRİNOLOJİ İLAÇ KULLANIMI: TÜRKİYE SAĞLIK BAKANLIĞI BİLGİSAYAR KAYITLARININ RETROSPEKTİF BİR ANALİZİ

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**ABSTRACT**

**Objectives:** "Off-label" is defined by the Turkish Ministry of Health as the use of licensed pharmaceutical products in doses outside the scope of the registered indication and the use of unlicensed medicinal products that are imported for the purpose of individual treatment. Aim of the study is to evaluate the use of off-label or unlicensed endocrinology medicines.

**Method:** A computer search was performed of the IEGM's (General Directorate of Pharmaceutical and Pharmacy-Ilac ve Eczacılık Genel Mudurlugu) database. Outcomes were evaluated in the light of indications for use.

**Results:** The computer search showed that 357 applications were submitted for off-label endocrinology medicine use. The highest application percentage was for osteoporosis (43%, 155/357). The highest application of osteoporosis occurred in the Ankara province (28%, 44/155). University hospitals had the highest off-label osteoporosis medicine applications within the given timeline (65%, 102/155). Specialized physicians in the fields of endocrinology and metabolism (adult and pediatric) had the highest number of off-label osteoporosis applications (71%,

111/155). The highest application percentage for off-label osteoporosis treatment was for teriparatide (87%, 136/155). Of the 136 applications, 92 were approved.

**Conclusion:** It could be said that off-label use can lead to reimbursement restrictions in endocrinology, especially for teriparatide.

**Keywords:***off-label;endocrinology; osteoporosis.*

## ÖZET

**Amaçlar:** Endikasyon Dışı" Türkiye Sağlık Bakanlığı tarafından, lisanslı ürünlerin onaylı endikasyonu ve dozu dışında kullanımı ve lisansı olmayan ancak bireysel olarak ithal edilecek tıbbi ürünlerin kullanımı olarak tanımlanmıştır.

**Yöntem:** IEGM veri bankasında bir bilgisayar taraması yapılmıştır. Sonuçlar kullanılan endikasyonlara gore değerlendirilmiştir.

**Bulgular:** Endikasyon dışı endokrinoloji ilaç kullanımı için 357 başvuru yapıldığı gözlenmiştir. Tüm başvurular içerisinde en yüksek başvuru yüzdesi "osteoporoz" tarafından sağlandığı gözlenmiştir (%43, 155/357). En yüksek başvuru yüzdesi Ankara ilinden gerçekleşmiştir (%28, 44/155). Endikasyon dışı osteoporoz ilaç kullanımı en yüksek başvuru üniversite hastanelerinindir (%65, 102/155). Endokrinoloji ve metabolizma (Erişkin ve pediatrik) alanında uzman hekimler en yüksek endikasyon dışı osteoporoz başvuru oranına sahiptir (%71, 111/155). Tüm osteoporoz başvuruları içerisinde en yüksek başvuru yüzdesi "teriperatidin osteoporozda kullanımı" için yapıldığı gözlenmiştir (%87, 136/155). 136 başvurunun 92`si onaylanmıştır.

**Sonuç:**Endikasyon dışı kullanımının özellikle teriperatid için geri ödeme kısıtlamalarını yönetimi amacıyla kullanıldığı söylenebilir.

**Anahtar Kelimeler:** *endikasyon dışı;endokrinoloji; osteoporoz.*

## INTRODUCTION

Off-label use is the practice of prescribing pharmaceuticals for an unapproved indication for use or in an age group outside of an approved indication for use, dose, or method of administration (1). The principles underlying the use of unlicensed medicines are the same as those of off-label medicines. Situations may occur in which a physician has used all normal treatment options and off-label and/or unlicensed medicinal products may be the last options (2).

Regulation of off-label use has different procedures in different countries. Physicians in the United Kingdom or United States (US) can prescribe medications off-the-label. In the United Kingdom, off-label prescriptions must serve the patient's needs better than the alternatives and must be supported by evidence or experience that demonstrates safety and efficacy to the British General Medical Council, (3). In the US, Medicare is required to cover the off-label use of a cancer pharmaceutical if it is in the pharmaceutical compendia or is supported by peer-reviewed articles in certain journals stated by Medicare. This implementation became law 12 years ago with the passing of the Rockefeller–Levin Bill. Named after its sponsors Senator Jay Rockefeller and Representative Sander Levin, the bill was passed as part of the Omnibus Reconciliation Act of 1993 (4).

Off-label use of medications is extremely common. Generic pharmaceuticals generally have no sponsors as their indications for use expand and incentives to initiate new clinical trials to expand indications for proprietary pharmaceuticals are limited (1). In one study, it was reported that 55% of prescriptions were licensed, 19% were unlicensed, and 26% were licensed pharmaceuticals used through off-label policies. In fact, unlicensed preparations were used in 40% of prescriptions for cytotoxic agents due to a lack of commercially available

formulations suitable for the pediatric patient (5).

Off-label use of medications is also public policy in Turkey in such that off-label use may lead to reimbursement restrictions. Off-label is defined by the Turkish Ministry of Health (MoHT) as the use of licensed pharmaceutical products in doses outside of or exceeding the scope of the registered indication and the use of unlicensed medicinal products that are imported for the purpose of individual treatment. Hence, off-label use covers both licensed and unlicensed products (6).

In Turkey, physicians can prescribe medications off-label or unlicensed under the control of the Ministry of Health Directorate-General of Pharmaceuticals and Pharmacy (IEGM) (http:// www.iegm.gov.tr). The IEGM evaluates off-label and unlicensed medication use for each patient through off-label application procedures. A treating physician who wants to prescribe an off-label or unlicensed pharmaceutical has to apply to the IEGM for patient-based approval. The IEGM then evaluates each application based published scientific evidence and academic consultants. If the IEGM approves the off-label or unlicensed prescriptions, the cost of medication subject to these prescriptions shall be reimbursed by the Turkish Social Security Institution (SGK) (http://www.sgk.gov.tr). When an unlicensed medicine is approved by the IEGM, the Turkish Pharmacy Association is then responsible for importing it (2).

The IEGM is responsible for the regulation of medicines in Turkey. Reimbursement decisions are given by committees consisting of representatives of the IEGM, SGK, and the Ministry of Finance. Usually, approved indications for use are evaluated and cascaded by these committees. Reimbursement decisions, which cover the whole country's use, are published by the SGK on its official web site. Thus, two indications for use (one for regulation and one for reimbursement) are addressed.

The IEGM also publishes guidelines for using pharmaceuticals without the patient base approval process. If a pharmaceutical is mentioned in these guidelines for use in an off-label indication not yet approved, physicians can prescribe it. The pharmaceutical will then be reimbursed by the SGK in the off-label indication without approval process. This indication is mentioned as "no-need to approval process off-label indications" in the guideline. No-need to approve process helps to increase the efficiency of off-label use decrease the workload of the IEGM.

In the analysis, the use of off-label or unlicensed endocrinology medicines were evaluated to provide an understanding of Turkey's perspective within this area of healthcare provisions. In addition, it was aimed to help update the guidelines and determine pharmaceuticals and off-label indications for no-need to approve process off-label indications in endocrinology pharmaceuticals.

## MATERIALS AND METHODS

A computer search was performed using the IEGM's database. The patient base was searched for off-label endocrinology medicine applications from June 19, 2009 to June 19, 2010. Outcomes were evaluated based on indications for use. The results were further evaluated according to the highest percentage of applications (e.g., pharmaceutical, patient situations). Applications were evaluated based on the hospital category, specialty of physician, provinces, medicine, patient demographics, patient clinic situation, and decisions on application dossiers.

Advanced evaluation with the pharmaceutical which had the highest percentage in the highest determined indication was conducted. In addition, the approval and rejection criteria were analyzed for the pharmaceutical that had the highest percentage in the indication. Total sales figures of pharmaceuticals from associated pharmaceutical firms in the same timeline were taken from Intercontinental Marketing Services (IMS)

Turkey and compared to the approvals given by the IEGM.

## RESULTS

The computer search for the dates falling in between 19 June 2009 and 19 June 2010 showed that 357 applications were submitted for off-label endocrinology medicine use. It was concluded that the highest application percentage was established by "osteoporosis" in all of the applications (43%, 155/357). Osteoporosis was followed by acromegaly (40), osteogenesis imperfecta (21), hyperparathyroidsm (14) and hypoparthyroidism(13), respectively. (**Table 1**).

| Disease | Number of Applications |
|---|---|
| Osteoporosis | 155 |
| Acromegaly | 40 |
| Osteogenesis imperfecta | 21 |
| Hiperparathyroidism (Primary&secondary) | 14 |
| Hipoparahyroidism (Primary&secondary) | 13 |
| Paget Disease | 9 |
| Puberty Abnormalities | 8 |
| Turner Syndrome | 8 |
| Hypophysis adenoma (TSH releasing) | 7 |
| Growth Hormone Deficiency | 6 |
| Cushing Sendrom | 5 |
| Others | 71 |
| Total | 357 |

***Table 1:*** *Numbers of Applications for Off-label Medicine Use in Different Disease Areas.*

As the most common application, the osteoporosis results were further evaluated. The average timeline of response from the IEGM to the applications were 11.44 ± 8.52 days. The highest application was from the Ankara province (28%, 44/155). This was followed by Istanbul, Bursa, and Izmir (39, 17, and 12, respectively). The other provinces had a combined 44 applications (**Table II**).

| Province | Number of Applications |
|---|---|
| Ankara | 44 |
| Adana | 4 |
| Afyon | 2 |
| Afyonkarahisar | 2 |
| Antalya | 1 |
| Aydin | 3 |
| Bursa | 17 |
| Denizli | 4 |
| Düzce | 1 |
| Edirne | 1 |
| Eskişehir | 1 |
| Hatay | 3 |
| Isparta | 1 |
| Istanbul | 39 |
| İzmir | 12 |
| Kayseri | 4 |
| Kocaeli | 2 |
| Malatya | 3 |
| Manisa | 3 |
| Mersin | 4 |
| Samsun | 3 |
| Trabzon | 1 |

***Table 2:*** *Osteoporosis Applications from Vaious Provinces.*

The highest approved application percentage was established by Istanbul province (76%). This percentage was followed by Izmir (75%), Ankara (71%), other provinces (66%), and Bursa (64%).

University hospitals had the highest off-label osteoporosis medicine use applications within the given timeline (65%, 102/155). This was followed by education and research hospitals, community hospitals, and private hospitals (28, 20, and 3, respectively) (**Table III**). The highest approved application percentage was established by private hospitals (100% approved). This was followed by university hospitals (73%), government hospitals (70%), and education and research hospitals (64%).

| Hospital Category | Number of Applications |
|---|---|
| University Hospital | 102 |
| Education&Research Hospital | 28 |
| Goverment Hospital | 20 |
| Private Hospital | 5 |

***Table 3*** *Hospital Categories in Osteoporosis Applications.*

The applications by province were further broken down by hospital category. Of Ankara province's 44 applications, 27 came from university hospitals. This was followed by 14 applications from education and research hospitals and 3 applications from private hospitals. The Istanbul province's 39 applications, 32 were from university hospitals. This was followed by

7 applications from education and research hospitals. In the Bursa province, 11 applications were from community hospitals and 6 were from university hospitals. In the Izmir province, 10 applications were from university hospitals and 2 were from education and research hospitals. From the other provinces, 27 applications were from university hospitals. This was followed by 10 applications from community hospitals and 5 applications from education and research hospitals.

Based on province, the highest university application rate was established by Izmir (83%). This was followed by Istanbul (82%), Ankara (61%), and Bursa (35%). The remaining provinces account for the remaining 64% (**Figure 1**).

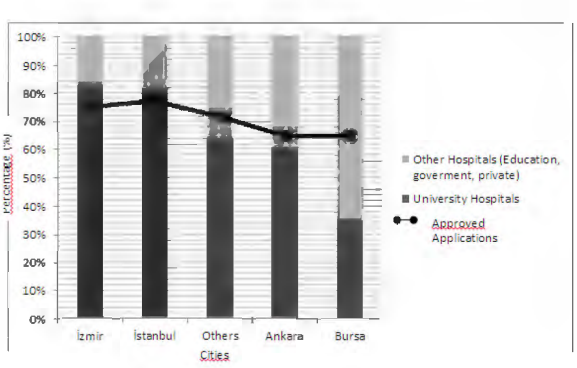


***Figure 1:*** *Distrubution of Hospitals and Approved Applications.*

Specialized physicians in the fields of endocrinology and metabolism (adult and pediatric) had the highest number of off-label osteoporosis applications (72%, 111/155). This was followed by physical therapy and rehabilitation and other areas of expertise (15% and 13%, respectively). The highest approved application percentage was established by specialized physicians in the fields of endocrinology and metabolism (74%). This was followed by specialized physicians in the fields of physical therapy and rehabilitation (62%) and other fields of expertise (50%).

The patient number is different from the application number, as some patients have multiple applications. The real patient number is 124. Demographic characteristics of patients with osteoporosis are mentioned in Table IV. Of the patients, only 2 were under the age of 18 and their overall diagnosis was juvenile osteoporosis.

| | |
|---|---|
| Age | 64,92±19,19 |
| Male | 43 |
| Female | 81 |
| Total | 124 |

***Table 4:*** *Demographics relating to osteoporosis patients.*

Of all the osteoporosis applications, the highest percentage was for the use of teriparatide (87%, 136/155) (**Table 5**).

| Medications | Number of Applications |
|---|---|
| Alendronate | 6 |
| Ibandronic acid | 1 |
| Dapsone | 1 |
| Pamidronate | 4 |
| Calcitriole | 1 |
| Morphine&Fentanyl | 1 |
| Risedronate | 2 |
| Calcitonin | 1 |
| Zolendronic acid | 3 |
| Teriparatide | 136 |

***Table 5:*** *Off-label Medications for Osteoporosis in All of the Applications.*

Of the 136 applications for teriparatide, 92 were approved. The highest reason for rejection was given as "not to use standard treatment alternatives which are available at the time of submission in Turkey" (**Table 6**).

| Reasons | Number |
|---|---|
| Standart treatment options for osteoporosis was not tried yet | 27 |
| Missing documents | 6 |
| Benefits of previously used off-label teriparatide were not documented | 5 |
| Application by patient relatives | 1 |
| Treatment deemed to be planned for the reason of secondary osteoporosis | 1 |

***Table 6:*** *Reason for Rejections in Teriparatide Applications.*

Even, patients of all approved applications had a fracture in any bone, applications for 30 patients who had fracture was rejected. The highest osteoporosis indication for teriparatide is stated as osteoporosis (49/136). This was followed by postmenopausal osteoporosis

and senile osteoporosis (32 and 18, respectively) (**Table 7).**

| Indication | Number of Applications |
|---|---|
| Osteoporosis | 49 |
| Postmenopausal Osteoporosis | 32 |
| Senile Osteoporosis | 18 |
| Secondary Osteoporosis | 14 |
| Medicines | 8 |
| Disease | 5 |
| Maternity | 1 |
| Idiopathic Osteoporosis | 5 |
| Juvenile Osteoporosis | 2 |

***Table 7:*** *Indications of osteoporosis in teriparatide applications.*

There was a significant difference between the T score (L1-4) of rejected and approved applications for patients (3.07 ± 1.85 and 3.23 ± 1.63, respectively) ($p < 0.001$). However, no significant difference was seen for the ages of patients for whom applications were rejected or approved. Although 25 applications for teriparatide use in male osteoporosis patients were approved, 11 were rejected. There was not a significant difference between the T score (L1-4) of the rejected and approved applications for male patients.

Of the applications, 24 applications for patients who had benefitted from previous teriparatide treatment were approved, whereas 8 were rejected. In addition, 38 applications for patients who had not benefitted from previous teriparatide treatment were approved, whereas 18 were rejected. There was not a significant difference between previous benefit from teriparatide treatment in rejected and approved applications for patients.

The monthly dose of teriparatide for osteoporosis is 20 mcg (7). All of the approved applications for using teriparatide were for 6 months at the same dosage. If the dosage regimens of all approved applications were to be used, 552 teriparatide injection pens would be used for 92 approved applications within the given timeline. Reimbursement price of one teriparatide pen is US $360 (US $1 = 1.5 TL) (www.sgk.gov.tr). Hence, the total cost corresponding to 92 applications would be nearly US $198,720. For normal and off-label use, 8,500 teriparatide injection pens were used in this time span; thus, it can be said that 6.4% of teriparatide sales depend on off-label use.

## DISCUSSION

The IEGM is responsible for the regulation of medicines in Turkey. Reimbursement decisions are given by committees consisting of representatives of the IEGM, SGK, and the Ministry of Finance. Usually approved indications for use are evaluated and cascaded by these committees. Reimbursement decisions, which cover the whole country, are published by the SGK on its official web site. Thus, two indications for use (one for regulation and one for reimbursement) are addressed.

A T-score of -2.5 or below indicates osteoporosis (8). However, the reimbursed indication for use for teriparatide is "≥ 65 year old patients with a ≤ -4 T-score (total L1-L4) and ≥ 2 fracture in Turkey." If a patient does not reveal these findings and teriparatide use is found necessary, the physician needs to make off-label applications to be reimbursed for the treatment.

Teriparatide was administered to patients 65 years or older who had a T-score of -4.0 or below, or a T-score of -3.5 or below, plus more than two fractures, or to those 55–64 years old who had a T-score of -4 or below, plus more than two fractures based on the National Institutes of Clinical Excellence (NICE) (9). In addition, teriparatide was reported to reduce vertebral and non-vertebral fracture risk markedly in women and men with idiopathic osteoporosis or with glucocorticoid-induced osteoporosis. This indicates that teriparatide should be considered as a first line treatment for postmenopausal women and for men with severe osteoporosis (10). However, there is no published

analysis for Turkey about teriparatide's cost-effectiveness in osteoporosis; it was only reported as a cost-effective option in osteoporosis when compared to no treatment (11).

It was noted that for the approved applications, the patients` average T-score was 3.23 ± 1.63 and the average age was 68.01 ± 15.88 for teriparatide use in osteoporosis. All approved patients had two or more fractures. This means that the committee for off-label endocrinology medicine in the IEGM approves higher T-scores than does the reimbursement T-score threshold that was published by the SGK.

In the light of these data, it can be said that T-score threshold for reimbursement of teriparatide use can be higher than -4, namely -3.2 or -3.5, for patients who are 65 years or older and have 2 or more fractures, as so with NICE`s offer. Therefore, the reimbursement restriction should to be updated by the SGK or new teriparatide use should be described in the no-need to approval process off-label indications by the IEGM. If the change were to occur, the workload for endocrinology off-label evaluation would decrease by nearly 28% (92/324) and more patients who are in real need for teriparatide may be able to access teriparatide through reimbursement. This may lead to decrease in cost, which depends on osteoporosis co-morbidities. Further analysis for calculating the cost for use by these patients is needed.

Although Istanbul is the largest province of Turkey with more than 12.5 million citizens (www.tuik.gov.tr), the highest number of applications came from the Ankara province. This difference was also seen in the Izmir and Bursa provinces. Although Izmir is the third largest province of Turkey with more than 3.7 million citizens, Bursa (2.4 million citizens) (www.tuik.gov.tr) had more applications.

The highest approved application rates were established in the Istanbul and Izmir provinces. Additionally, these provinces had the highest university hospital application rates. Ankara and the other provinces revealed similar yet lower application rates than those found in university hospitals across Istanbul and Izmir. These provinces established lower application approval rates. Bursa had the lowest university hospital application and application approval rates. Furthermore, the highest approved application rates were established by university hospitals in all hospitals. As university hospitals are noted as third step treatment centers by MohT, these hospitals usually treat patients with more severe diseases and conditions than those seen in patients at other hospitals.

There were 3832, 6314, and 9114 (estimated) applications for using off-label oncology medicines in Turkey for the years 2008, 2009, and 2010, respectively (10). Off-label medicine use applications are rising every year. This may be due to the increasing awareness of off-label use with physicians able to access scientific literature immediately via the Internet. In addition, it may be due to the physicians and pharmaceutical companies trying to avoid reimbursement procedures of the SGK by making use of the IEGM off-label use procedures (2). The exact reasons of the increase in application numbers through the years cannot be determined with these findings. Further study is needed to evaluate the reason of increasing applications numbers in recent years.

Off-label use can lead to reimbursement restrictions in endocrinology, especially for teriparatide-like oncology medicines. In Turkey, physicians who want to prescribe an off-label or unlicensed pharmaceutical or a medicine that has a different use from reimbursement indications need to apply through the off-label medicine use process. This analysis showed that there is a vast amount of off-label endocrinology medicine applications in Turkey. Further analyses need to be done in different disease areas and medicines.

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