Spotlight on... *Medicinal products for rare diseases in Turkey*

Interview

In November 2008, Turkish pharmacist Pelin Kilic joined the team of Orphanet France in order to pursue her PhD studies in gene technology, specifically in the area of rare diseases, under the scope of a national government scholarship programme offered by the Turkish Ministry of Health. Ms. Kilic officially holds a position at the Turkish Ministry of Health Directorate General of Pharmaceuticals and Pharmacy, which she will resume upon her return to Turkey. Recently, she described for *OrphaNews Europe* the current situation of patient access to orphan medicinal products in Turkey.

*OrphaNews Europe*: How are orphan medicinal products categorised in Turkey?

**Pelin Kilic**: At present, the Turkish Ministry of Health (MOH) has not yet developed a national policy with reference to “rare diseases” and “orphan drugs”, as commonly defined inside the European Union (EU). Therefore, patients suffering from known rare diseases in Turkey access treatment with nationally licensed or non-licensed human medicinal products that have been granted marketing authorization (MA) by the European Medicines Agency (EMEA) under “orphan designation” and/or indicated for the treatment of specific rare diseases.

*OrphaNews Europe*: Could you comment on the regulation(s) under which medicinal products are registered in Turkey?

**Pelin Kilic**: In Turkey, licensing applications for all human medicinal products are submitted, by accredited license holders, to the Directorate General of Pharmaceuticals and Pharmacy (DGPP) operating under the MOH, in line with the “Regulation on Licensing for Medicinal Products for Human Use” (I shall hereafter refer to it as the “Regulation”).

*OrphaNews Europe*: How much compliance does Turkish regulation hold with regard to the
EU Legislation?

_Pelin Kilic_: The mentioned Regulation, currently in force has been adapted by the DGPP in accordance with the European Commission (EC) Directive 2001/83/EC placed under the EU Legislation related to medicinal products for human use. It is also based on the national Law No. 1262 for Pharmaceutical and Medicinal Preparations along with these items:

i) Article 3(k) of the Basic Law No. 3359 for Medicinal Services,

ii) Article 8 of the Law No. 2857 on Blood and Blood Products, and

iii) Article 43 of the Ministerial Decree No. 181 governing the Organization and Responsibilities of the Turkish MOH.

_OrphaNews Europe_: What kind of scientific evaluation processes are implemented for licensing applications?

_Pelin Kilic_: During the scientific and technological evaluation periods of pre-licensing, licensing applications are passed through several phases of Advisory Committees for efficacy, reliability and quality assessments in approval, listed below:

- Advisory Committee dedicated to the Technological and Pharmacological Evaluation of Human Medicinal Products
- Advisory Committee dedicated to the Bioavailability and Bioequivalence Evaluation of Human Medicinal Products
- Advisory Committee dedicated to the Evaluation of Human Medicinal Products.

_OrphaNews Europe_: What happens at the stage of post-licensing?

_Pelin Kilic_: Once granted a license, the name of the specific license holder and the product license number is issued in the Turkish Official Gazette. Such an issued license approval shall be deemed valid for a standard period of five consecutive years thereafter, unless suspended or cancelled. Licensing renewal for a consequent period of another five years for medicinal products is submitted together with pharmacovigilance data containing information regarding efficacy, reliability and quality criteria to the opinion of the Advisory Committee for the Safety Monitoring and Evaluation of Medicinal Products for Human Use. Under these circumstances, risk/benefit analyses are performed under the rules laid down by the Pharmacovigilance Regulation of Medicinal Products for Human Use.

_OrphaNews Europe_: Are such medicinal products placed on the Turkish pharmaceutical market immediately following their license approvals?

_Pelin Kilic_: Sales permission of licensed medicinal products is granted to license holders for the first time only after the evaluation of finished market packaging samples of products.

_OrphaNews Europe_: Are there any exceptions to cases such as orphan medicinal product licensing?

_Pelin Kilic_: As I have already mentioned, we do not yet recognise such medicinal products, and therefore, do not implement procedures such as fast-track evaluation. However, scientific evaluation of such products may yield some privileges under certain circumstances:
- Therapeutic indications are so limited that the applicants are reluctant to provide detailed evidence;
- Detailed information is limited in the context of existing scientific information (this may certainly be the case if such indications include rare diseases);
- Collection of such information holds the risk of violating ethical principles.

**OrphaNews Europe:** Is data exclusivity recognised in your provisions?

**Pelin Kilic:** Yes. The period of data exclusivity determined for medicinal products in Turkey, without prejudice to the provisions of the Decree No. 551 regarding the Protection of Patent Rights dated 24 June 1995, is six years.

**OrphaNews Europe:** Are there any exceptions in patient access to treatment with medicinal products?

**Pelin Kilic:** Medicinal products, licensed, and only such, which have been scientifically indicated as efficient and safe in the treatment of specific diseases, are readily accessed by patients in Turkey. Besides, the DGPP has set standard rules and regulations concerning off-label use and/or use of doses exceeding the indicated limits of licensed medicinal products, and for import of non-licensed medicinal products.

**OrphaNews Europe:** How do patients access imported non-licensed medicinal products?

**Pelin Kilic:** Following the provisions of the Law No. 1262 for Pharmaceutical and Medicinal Preparations, the Turkish Pharmacists’ Association (otherwise known as “TEB”) conserves the responsibility of following import procedures of non-licensed medicinal products.

**OrphaNews Europe:** How do pharmacoeconomical processes (pricing/reimbursement) work in your country?

**Pelin Kilic:** An ad hoc Advisory Committee dedicated to the Pharmacoeconomical Evaluation of Human Medicinal Products meets to conduct DGPP pricing evaluation of all medicinal products. Here, suitable pricing analyses based on the Reference Countries Price List are made for original and generic medicinal products. All necessary evaluation is concluded within a 10-day period upon dossier submission from pharmaceutical companies. Thereon, these dossiers are forwarded to the final opinion of the permanent Pricing Evaluation Commission, which meets regularly under the coordination of the MOH every three months. All prices are issued on the DGPP official website, immediately after. The Reimbursement Commission gets together each September under the coordination of the Ministry of Finance in order to evaluate the cost-effectiveness of the medicinal products. Once approved, such products are included in an official “positive list” for the following year to be either completely or substantially reimbursed. Both licensed and imported products may be subject to reimbursement evaluation if deemed necessary. Products are usually not removed from the positive list unless a serious outcome (i.e. adverse drug event – ADR – signalization) is reported.
OrphaNews Europe: Are there any initiatives under towards the recognition of rare diseases and orphan medicinal products in Turkey?

Pelin Kilic: The MOH has recently started collaboration with Orphanet-Turkey in specific projects for the establishment of a National Plan for Rare Diseases. Orphanet-Turkey, based at the Istanbul University Experimental Medical Research Institute Department of Genetics, was launched towards the end of 2007. This project is currently sponsored by DG SANCO, and runs under the Coordination of Prof. Dr. Ugur Ozbek, with Information Scientist Dr. Fatmahan Atalar and Assistant Scientist Bio. Ozge Ozgen.

Currently, numerous orphan medicinal products along with other products indicated for treatment of rare diseases are provided for the treatment of patients in Turkey, including licensed products or non-licensed and imported ones. See Table 1 (List of Accessible Orphan Medicinal Products in Turkey as of January 2009), Figure 1 (Distribution of Imported vs. Licensed Orphan Medicinal Products in Turkey), Figure 2a (Distribution of Orphan Medicinal Products in Turkey by ATC Code) and Figure 2b (Imported vs. Licensed Comparison of Orphan Medicinal Products in Turkey). These *graphics illustrate the current situation of orphan medicinal product accessibility in Turkey. Finally, detailed information on medicinal products for all diseases in Turkey is available on the DGPP official website (in Turkish language). An overview of the Turkish Regulation on Licensing of Human Medicinal Products is also available in English language.

Table 1: List of Accessible Orphan Medicinal Products in Turkey as of January 2009

<table>
<thead>
<tr>
<th>INN</th>
<th>Trade Name in Turkey</th>
<th>Indication(s) for Use</th>
</tr>
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<tbody>
<tr>
<td>agalsidase beta</td>
<td>FABRAZYME</td>
<td>Fabry disease</td>
</tr>
<tr>
<td>anagrelide</td>
<td>THROMBOREDUCTIN</td>
<td>Hepatic veno-occlusive disease</td>
</tr>
<tr>
<td>bosentan</td>
<td>TRACLEER</td>
<td>Pulmonary hypertension</td>
</tr>
<tr>
<td>busulfan (i.v.)</td>
<td>BUSULFEX, MYLERAN</td>
<td>Leukemia (myeloid, acute)</td>
</tr>
<tr>
<td>carglumic acid</td>
<td>-</td>
<td>Hyperammonmonemia</td>
</tr>
<tr>
<td>cladribine</td>
<td>-</td>
<td>Leukemia, hairy cell</td>
</tr>
<tr>
<td>dapsone</td>
<td>-</td>
<td>Dermatitis herpetiformis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Behcet disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lupus erythematosus (discoid; systemic)</td>
</tr>
<tr>
<td>dasatinib</td>
<td>SPRYCEL</td>
<td>Leukemia (myeloid, chronic; lymphoblastic, acute)</td>
</tr>
<tr>
<td>deferasirox</td>
<td>EXJADE</td>
<td>Beta-thalassemia; Sickle cell anemia</td>
</tr>
<tr>
<td>eculizumab</td>
<td>-</td>
<td>Paroxysmal nocturnal hemoglobinuria</td>
</tr>
<tr>
<td>galsulfase</td>
<td>-</td>
<td>Mucopolysaccharidosis type 6</td>
</tr>
<tr>
<td>ibuprofen</td>
<td>-</td>
<td>Patent arteriosus ductus anomalies (Arterial duct anomaly)</td>
</tr>
<tr>
<td>iloprost</td>
<td>VENTAVIS</td>
<td>Acute peripheral arterial occulsion</td>
</tr>
<tr>
<td>imatinib</td>
<td>GLIVEC</td>
<td>Leukemia (myeloid, chronic; lymphoblastic, acute)</td>
</tr>
<tr>
<td>miglustat</td>
<td>ZAVESCA</td>
<td>Gaucher disease</td>
</tr>
<tr>
<td>pegvisomant</td>
<td>SOMAVERT</td>
<td>Acromegaly</td>
</tr>
<tr>
<td>sorafenib</td>
<td>NEXAVAR</td>
<td>Renal cell carcinoma (metastatic)</td>
</tr>
<tr>
<td>sunitib maleat</td>
<td>SUTENT</td>
<td>Renal cell carcinoma (metastatic)</td>
</tr>
<tr>
<td>thalidomide</td>
<td>THALIDOMIDE-PHARMION</td>
<td>Myeloma, multiple; Myelodyplastic syndrome</td>
</tr>
</tbody>
</table>
Figure 1. Percentage Distribution of Imported vs. Licensed Orphan Medicinal Products in Turkey (January 2009)

Imported (n=6) 35%
Licensed (n=13) 65%

Figure 2a. Percentage Distribution of Orphan Medicinal Products in Turkey by ATC Codes (January 2009)

- Alimentary Tract and Metabolism (ATM) 11%
- Antineoplastic and Immunomodulating Agents (AIA) 21%
- Cardiovascular System (CS) 5%
- Blood and Blood Forming Organs (BBFO) 5%
- Systemic Hormonal Preparations, Excl, Sex Hormones (SHPESH) 5%
- Various (V) 11%
- Unclassified (U) 42%
Figure 2b.
Imported vs. Licensed Comparison of Orphan Medicinal Products in Turkey by ATC Codes (January 2009)

*Graphics data have been compiled from: i) Pricing List of All Medicinal Products, updated official release dated 09 January 2009; ii) List of Imported Drugs in Turkey, updated official release dated 20 June 2008; iii) Other relevant information found on the official website of the DGPP).

All individuals interested in further information are welcome to contact Pelin Kilic:

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