

Newsletter 17

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Welcome note

Dear readers,

Welcome to the 17th issue of our Newsletter where we present our associates in Croatia, our Marketing Manager and our product Olanzapine.

In our Eco-friendly tips we report on the growing problem of noise pollution, whilst schizophrenia is the topic under Health Matters.

We explain the term "Quality Control" and report on various topics of Corporate Social Responsibility and other company news.

We also include a feature article on the new guidelines for Good Distribution Practice.

Finally, we take a glimpse at the picturesque village of Lefkara.



Charalambos Pattihis,
Group Managing Director

Regulations or Feature Article: Good Distribution Practice

The pharmaceutical industry of the European Union adheres to high quality standards that are set out as guidelines for Good Manufacturing Practice (GMP) which are applied to all products that are manufactured under its marketing authorisation licences.

An appropriate level of quality must be maintained not only during manufacture but also throughout the whole supply network in order to ensure that pharmaceutical products will be distributed without any detriment to or ownership of this quality. Once a product has been released into the market, wholesalers must comply with Current Good Distribution Practice (cGDP) which requires them to operate a quality system which is sufficiently robust to ensure that pharmaceutical products are stored, handled and distributed under conditions that will ensure their quality. As a consequence these guidelines cover the whole supply network and all staff must be qualified and empowered to enforce these standards. They must ensure that the quality of medicinal products and the integrity of the distribution chain are maintained throughout the distribution process so as to prevent the introduction of falsified products and be capable of dealing with any consequent recall incidents.

Premises and equipment used throughout the supply chain are evaluated and rated to ensure that they meet the required standards to secure the quality of the medicinal product. All participants including employees, partners, and customers must undergo specific training in relation to good distribution practices in order to establish a common understanding and thus facilitate the

creation of standard operating procedures or quality agreements.

The biggest piece of the pie is given to the physical transportation of the product. All transportation methods, packaging solutions, supply chain routes and the duration of the delivery period are evaluated in respect of their capability to ensure that product will be handled, stored and transported under the proper conditions. Throughout the whole supply chain, all operatives are obligated to monitor and control the conditions under which the product is being moved or temporarily stored.

Examples of some actions covered by the Current Good Distribution Practices are:

- Qualification of the packaging solution used to ensure that it is capable of creating conditions that will maintain the specified quality of the medicine.
- Qualification of the means used to transport the medicinal product to show that it will maintain the specified conditions throughout the whole supply chain.



- Qualification of all the elements of the supply chain to confirm that the quality system set down will ensure that the medicinal product will be stored, handled and distributed under the proper conditions.

- Use of temperature and humidity data loggers to monitor the conditions under which the medicinal product is being stored, handled and distributed.

The primary objective of imposing the cGDP is to ensure that product quality is maintained

throughout the supply chain even if the product will need to be transported over long distances using a variety of transport systems and may thus be exposed varying climatic conditions on the journey to its destination.

cGDP must be considered by the manufacturer to be of equal importance to cGMP. It is the responsibility of the manufacturer cGDP and/or the holder of the marketing license authorisation to adopt

cGDP either as a trading member in the European Union or as a supplier/partner with a country outside the European Union. States like Saudi Arabia, Egypt and the rest of the Middle East and Africa (MENA) region have imposed their own regulations and strict standards relating to the overall supply chain of medicinal products throughout their countries. ■

Remedica worldwide: Alpha Medical d.o.o. Croatia

Croatia is Mediterranean country founded in 1991 after the breakup of Yugoslavia.



Croatia is member of the UN, NATO, the Organisation for Security and Cooperation in Europe, the Council of Europe, the World Trade Organisation and, in line with the result of a national referendum held in January 2012, will become an EU member in 2013. Croatia has borders with Italy, Slovenia, Hungary, Serbia, Montenegro, Bosnia and Herzegovina. Croatia has a coastline that is 1,777 km long not including that of its 1185 offshore islands. Croatia is a parliamentary democracy with 4.55 million citizens: Zagreb is the capital city.

Alpha Medical was established in 1992 when members of the Dvoržak family returned from Germany where they had held various management positions in a multinational company. Alpha Medical is owned by Livia which also runs the chain of "Pharmacies Dvoržak" and is a partner in the company Zegin which in turn owns the largest pharmacy chain and the biggest pharmaceutical wholesaler in the Former Yugoslav Republic of Macedonia (FYROM).

Alpha Medical started to register Remedica products in 2005 and to date there are 3 Remedica products on the market which are distributed to all wholesalers and hospitals in Croatia. The company's Regulatory Affairs department is currently preparing licence applications for three more Remedica products. ■



Our Products: Olanzapine-Remedica

Our product Olanzapine-Remedica tablets contains the active substance olanzapine.

Olanzapine is an antipsychotic agent that belongs to the thienobenzodiazepine class of compounds. It is a monoaminergic antagonist which binds with high affinity to serotonin muscarinic, histamine-H₁, adrenergic (α₁) and the dopaminergic receptors in the central nervous system. Olanzapine, after oral administration, shows a peak in blood level concentration around 5-8 hours.¹

Olanzapine is a member of a group of agents which are often known as atypical antipsychotic drugs and is used to treat patients with acute psychosis, schizophrenia and moderate to severe mania.² It has also been approved for acute and long-term treatment of bipolar disorder and it has a relatively high safety profile in comparison with other classical antipsychotic medications.³

The therapeutic advantage of atypical antipsychotics like olanzapine is a consequence of its ability to act on a range of receptors such as those with dopaminergic, serotonergic, muscarinic and adrenergic activities.⁴ It has a receptor profile similar to that of clozapine, but generally exhibits fewer side effects.⁵

Olanzapine has beneficial effects on cognitive impairment and neuropathological changes when used to treat neurodegenerative diseases and has superior therapeutic efficacy against the negative symptoms of schizophrenia, when compared with the typical neuroleptics.⁶

Antipsychotics have become the drugs of choice for the treatment of schizophrenia. Recent emerging biochemical data has indicated that several important neuroregulatory genes and proteins may be involved in the aetiology of schizophrenia and

bipolar disorder. Interestingly, these same genes appear to be targets for several of the psychotropic medications that are used to treat such disorders. For example one study showed that olanzapine causes changes in levels of several important genes that may be involved in the etiology and, by implication, the treatment of schizophrenia and other psychiatric disorders.⁷

In addition, a novel mechanism of action has been proposed for olanzapine involving stimulation of the mitogen-activated protein kinase pathway.⁸

Olanzapine-Remedica is available in 5mg, 10mg and 15mg tablets. ■

References:

¹ Waring et al., 2006, PDR, 2007

² Martindale, 2005, Waring et al., 2006, PDR, 2007

³ Tamam and Annagur, 2006

⁴ PDR, 2007

⁵ Lindenmayer and Patel, 1999

⁶ Ohashi et al., 2000

⁷ Fatemi et al., 2006

⁸ Fumagalli et al., 2006

Health Matters:

Schizophrenia

This is a mental disorder which affects the way in which the sufferer thinks, feels and behaves and is characterised by both positive and negative symptoms. Positive symptoms include delusions, commonly paranoid, hallucinations and voices which may talk to the patient or multiple ones which talk about the patient. Negative symptoms include a loss of interest in life, inability to concentrate, loss of normal feelings or emotions and difficulties in conducting social interactions and the patient becomes socially withdrawn. Men commonly show symptoms around the age of 20 with women presenting about 10 years later but the frequency of occurrence is equal in both sexes. Although only 1% of the population get schizophrenia and 10% of sufferers will have a parent with the disease, it is not thought to be entirely genetically based and a predisposed child can be prevented from presenting with symptoms if they are reared in the correct environment.

Since it is known that illicit substances like cannabis can cause the user to not only exhibit schizophrenic type symptoms but also induce the disease, diagnosis should not be carried out whilst the individual is using illicit drugs: the stronger forms of cannabis (e.g. skunk) may be more dangerous in this respect and all forms are more likely to cause problems if smoked by teenagers.

The diagnosis is often difficult because of the commonality of symptoms between the range of mental illnesses (psychoses), for example patients with bipolar disorder or severe depression may also have psychotic traits. In general schizophrenia is diagnosed if the patient has at least two of the following symptoms: - hallucinations, delusions or disorganised thought (which may result in speech which is confused and repetitive or difficulty in carrying tasks such as personal hygiene) and occurrence of negative symptoms. These symptoms should be observed for a major proportion of each month, persist for at least 6 months and should affect the ability of the individual to work or otherwise lead a normal life. Once diagnosed the condition is usually qualified as mild, moderate or severe. Schizophrenia can occur abruptly or the symptoms can develop slowly when friends and relatives are the most likely to detect a problem but not be able to put a name to it.

Treatment.

Fortunately, there are many drugs which can be used in the successful treatment of schizophrenia nowadays so much so that hospitalisation, if required, is usually short-term and not the 'life sentence' of former years. Since all psychotic diseases involve some element of increased activity of dopamine (the chemical which acts as a neurotransmitter) in the brain then most of the drugs block one or more dopamine receptors. Treatment can be given by the oral route as tablets or capsules but long-lasting injections are also available and are often used in patients who do not take their medicines properly. The antipsychotic drugs relieve positive symptoms more effectively than negative ones which often persist during periods when the positive ones have been controlled. Early treatment is always the most likely to be effective and patients with acute symptoms respond better than those with chronic ones.

First Generation Antipsychotic Drugs (FGAD).

These work by blocking the D_2 dopamine receptor in the brain but are not selective so a range of side effects can be induced, the most significant of which are those on the extrapyramidal system which



controls voluntary movement and balance: the most common examples are inability to initiate movement or to remain motionless.

Examples of this class of agents are promazine and chlorpromazine (Group 1), pericyazine and pipotiazine (Group 2) and trifluoperazine, fluphenazine and prochlorperazine (Group 3). These groupings are based upon potency and the severity of side effects. Haloperidol resembles Group 3 agents whereas flupentixol and sulpiride are in some ways similar to Groups 1 and 2.

Second Generation Antipsychotic Drugs (SGAD).

These act on a range of receptors (dopamine D_1 , D_2 , D_4 , 5-hydroxytryptamine_{2A}, histamine-, α -, adrenoreceptor) and as a result have a more defined action and induce less side effects. Examples include olanzapine, paliperidone, quetiapine, risperidone, clozapine and amisulpride. Although these agents produce fewer neurological side effects, more metabolic side effects such as weight gain and diabetes are apparent.

Choice of Therapeutic Regime.

The selection of therapy needs to be made on the basis of patient history and the likely side

effects as much as desired effects. Obviously if there is concern about the occurrence of extrapyramidal side effects then a FGAD should not be used whereas the patient has a high risk for diabetes then a SGAD would not be the drug of choice. The SGADs may be the drugs of choice if negative symptoms need to be controlled whereas Group 1 FGADs are more sedating. Whatever drug is chosen it should not be rejected as ineffective until it has been used for 4-6 weeks: the use of more than one antipsychotic drug at a time should be avoided.

All patients need to have full blood counts, urea and electrolytes monitored as well as liver function tests when therapy is started and annually thereafter. Patients taking clozapine must be registered with a patient monitoring service to check for any undesirable changes in white blood cell count on a weekly basis for 18 weeks and every 2 weeks thereafter.

Despite the risks associated with antipsychotic drugs used in schizophrenia, the results can be good and although therapy may have to be continued for many years a full recovery is possible but patients need to be encouraged to continue taking their medication even when they feel that they are better. ■





Eco-friendly tips: Noise Pollution

According to the European Protection Agency, environmental noise is simply defined as the unwanted or harmful sound which spreads both in duration and geographical coverage. Environmental noise refers to the noise associated with many human activities such as road, railway and air traffic, construction work and industrial noise as well as the that produced by a neighbourhood. It should be noted that the term environmental noise does not include the noise within a workplace area.

The extent and severity of environmental noise is a major environmental concern especially in urban areas as was reflected in the Green Paper on future noise policy in the European Union. This paper stated that around twenty per cent of the Union's population suffer from noise levels that scientists and health experts consider to be unacceptable. In addition, the Royal Commission on Environmental Protection suggested that environmental noise is considered to be a major problem for one in three households in the United Kingdom.

Noise can have a major impact on the health and wellbeing of individuals both directly and indirectly. According to the Royal Commission on Environmental Protection a persistent exposure to environmental noise could cause annoyance, stress and disturb sleep. What is remarkable is the fact that persistent exposure to noise above a certain level during both the day or night, can result in cardiovascular diseases.

An assessment conducted by the World Health Organisation showed that road traffic noise increases the risk of ischemic heart disease, including myocardial infarction. Moreover both road traffic and aircraft

noise can increase the risk of high blood pressure. Other studies have showed that environmental noise can induce adverse effects on mental health by increasing, for example, anxiety and aggressiveness among people who have to live in a noisy environment.

Apart from the effect on humans, environmental noise can also affect wildlife and ecosystems. Common effects include the reduction of habitat space due to the fact that many animal species cannot tolerate noise, thus many feeding and breeding grounds are not available to them any more. In addition, according to the European Environment Protection Agency many bird species change their migration routes in order to avoid noisy environments. As a result the risk of disorientation is increased leading to a reduced likelihood of survival and accessibility of feeding and breeding grounds.

Although environmental noise is a major concern, to date little has been done to adequately address it. The European Commission suggested that a framework with shared responsibility and target setting should be developed in order to mitigate environmental noise, but more action is necessary in order to achieve an effective and desirable outcome. ■



Corporate Social Responsibility: Remedica Cares

1) Earth hour. (photo 1)

In an attempt to contribute to the worldwide action to reduce of climatic change, Remedica reminded its staff to switch off all lights at home for an hour on the 31st March. The concept of Earth Hour which was proposed by the World Wide Fund for Nature (WWF) is a simple one that has quickly turned into a global phenomenon. It is hoped that hundreds of millions of people will all turn off their lights for one hour, on the same night, all around the planet. It is meant to emphasise the need appreciate the brilliant world that we all share and how we need to take positive action to protect it: not just for one hour a year, but every day.



2) Charity event for Greece. (photo 2)

Remedica held a collection amongst its staff and the money raised was used to buy 1 ton of foodstuffs for needy people in Greece. The consignment was sent through the Holy Archbishopric of Cyprus and was delivered by a Remedica representative to the Holy Bishoprics of Nicaea Attica and Piraeus, and will be used in "soup kitchens" set up by these two Bishoprics.



3) CSR focus Group of the Cyprus Chamber of Commerce and Industry.

Remedica's Andreas Hadjipanayis, who is in charge of matters relating to Corporate Social Responsibility (CSR), took part in a Focus Group Meeting held by the Cyprus Chamber of Commerce and Industry and the auditors Deloitte. In the meeting a specific presentation on CSR practices worldwide was made by Mr. Bill Marquard, Director at Deloitte of Chicago, USA, an expert on CSR topics, advisor to multinational companies and author of influential publications on strategy issues. The participants had the opportunity to exchange experiences and practices and to discuss CSR and other topics with Mr Marquard.



4) Easter candles.

As part of its support for non-profit organisations, Remedica purchased Easter candles for all its staff



from 3 different associations: the Day Centre for People with Special Needs (Prosvasi), the Theotokos Foundation and the Cyprus Association of Cancer Patients and Friends.

5) Blood donation. (photo 3)

Remedica held a blood donation session at its premises where many employees volunteered for this altruistic gesture that saves many lives every year.

6) Health and Safety Week. (photo 4)

On the occasion of World Health & Safety at Work Day (28th April 2012), Remedica carried out a week long awareness campaign (30th April to 5th May). During the campaign, Remedica's Health & Safety Officer provided information on a daily basis via e-mail and notices on electronic displays, on ways to avoid accidents. In addition, Remedica's TV screen in the staff canteen, displayed relevant presentations and videos.

7) Drugs and the Internet. (photo 5)

On Wednesday, 2/5/2012, Remedica organised a lecture on "Drugs and the Internet" for the company's employees. The aim of the lecture was to inform staff of the potential dangers of purchasing medicinal products through the internet.

8) Pan-Cyprian door-to-door collection by the local Red Cross. (photo 6)

This annual charity collection was held in order to raise funds for the various programmes and missions of the Cyprus Red Cross, both locally and abroad. Once again, Remedica contributed to these efforts by offering financial aid.

9) Participation in the European programme Responsible Med -TEPAK.

Remedica's Marketing Manager, Andreas Hadjipanayis, took part in a pilot study in connection with the European programme Responsible Med hosted by TEPAK (the Cyprus Technological University). The project was intended to evaluate the relationship between Corporate Social Responsibility, competitiveness level and innovation amongst Mediterranean corporations. ■

The ABC of Pharmacy:

Quality Control



Quality Control is that part of Good Manufacturing Practice which is concerned with sampling, specifications and testing, and with the organisation, documentation and release procedures which ensure that the necessary and relevant tests are actually carried out and that materials are not released for use, nor products released for sale or supply, until their quality has been judged to be satisfactory.

The basic requirements of Quality Control are that:

- i. adequate facilities, trained personnel and approved procedures are available for sampling, inspecting and testing starting materials, packaging materials, intermediate, bulk, and finished products, and, where appropriate, for monitoring environmental conditions for GMP purposes;
- ii. samples of starting materials, packaging materials, intermediate products, bulk products and finished products are taken by personnel and by methods approved by Quality Control;
- iii. test methods are validated;
- iv. records are made, manually and/or by recording instruments, which demonstrate that all the required sampling, inspecting and testing procedures were actually carried out. Any deviations are fully recorded and investigated;
- v. the finished products contain active ingredients complying with the qualitative and quantitative



composition of the Marketing Authorisation, are of the purity required, and are enclosed within their proper containers and correctly labelled;

vi. records are made of the results of inspection and that testing of materials, intermediate, bulk, and finished products is formally assessed against specifications. Product assessment includes a review and evaluation of relevant production documentation and an assessment of deviations from specified procedures;

vii. no batch of product is released for sale or supply prior to certification by a Qualified Person that it is in accordance with the requirements of the Marketing Authorisation;

viii. sufficient reference samples of starting materials and products are retained to permit future examination of the product if necessary and that the product is retained in its final pack unless exceptionally large packs are produced. ■



Remedica News

1. Remedica and the 6th Limassol International Marathon GSO. (photo 1)

Remedica took part in the 6th Limassol International Marathon GSO held on the 18th March with a corporate entry of 18 colleagues thereby making a significant contribution to the fund-raising effort. In total about 1000 runners took part and thousands more participated in the student run, the charity run or as mere spectators. Amongst them were also about a thousand overseas visitors who came especially to participate in this event. In addition to raising funds for charity aspect, the Marathon aims to spread spirit of sportsmanship, participation and volunteerism.

2. Social activities programme in promoting education. (photo 2)

Under the auspices of its social activities programme, Remedica hosted the pupils of the Lanition B High School of Limassol in an educational visit that included a tour of company facilities and gave the pupils the chance to be informed about career prospects in the pharmaceutical industry.

3. Visit from TEPAK.



Representatives from TEPAK (the Cyprus Technological University) headed by the Vice Chancellor Professor Andreas Anayiotos, visited Remedica and met the company's management. In addition to a tour of company facilities, the two parties discussed several issues of mutual interest including a protocol for closer collaboration on several topics. ■



Remedica People

In this issue we present our Marketing Manager Mr. Andreas Hadjipanayis.

After completing his studies in Business Management he began his career as Sales Executive in a cosmetics company where he soon undertook the duties of Assistant Marketing Manager / Export Manager and was finally promoted to Marketing Manager.

Since he was appointed as Remedica's Marketing Manager in 2005 he has been responsible for many activities such as marketing, sales, advertising and communication strategy within Cyprus.

In 2009, he cofounded the "Remedica Volunteer" team having as its main pillars Remedica's Corporate Social Responsibility Programmes on matters such as health, education, environment, society and culture.

He is a member of Remedica's strategy team, has served as both Vice-President and President of the Junior International Chamber

of Limassol, is a member of the Central Committee of the Cyprus Red Cross (Juniors' Section), has given lectures in colleges and seminars (on Corporate Social Responsibility, Sales, Customer Services etc.) and also taken part in training seminars and conferences in Cyprus and abroad.

He is married and has two children: he spends his free time with his family.

He takes great pride in the various awards presented to Remedica but always stresses that "they all belong to Remedica's employees and are a motivating force for even greater successes".

His personal vision over the next ten years is that he will be much richer in experiences with an even more positive outlook for a healthier world through Remedica's products, which will be more accessible and available to a larger



number of patients worldwide whilst at the same time, the company's charity and social work towards world society will be enhanced. ■

A glimpse of Cyprus: Lefkara

Lefkara a village lying on the south-eastern slopes of the Troodos mountain range at a level of 650m, only 12 km from the Lefkosia-Limassol main road, is considered to be the birthplace of Cyprus the lace and embroidery craft which is well-known throughout the world. Its name is attributed to the white lime stone which surrounds the village and "Lefkara" means "White Mountains" in the Greek language.

The first written reference to Lefkara is provided by a great figure in Cypriot literature in the Middle Ages, Saint Neofytos who reports in one of his works that he was born in Lefkara in the year 1134 A.D.

As a direct consequence of the excellence its lace making craft and trade, Lefkara became famous and gained much of its wealth and prosperity as early as the first decade of last century. Some researchers believe that the origins of Lefkara lace go back to Venetian times (1489-1570) when Lefkara was used to as a summer resort by Venetian nobles and their families. It is alleged that when the famous artist Leonardo da Vinci visited Cyprus at the end of the 15th century he took the opportunity to visit Lefkara and bought a large table-cloth, made entirely of lace, which he donated to the Duomo cathedral in Milan to be used as the altar cloth.

In 1878 Cyprus passed into British rule and in 1883 Lefkara was declared a municipality which had a tremendous impact on the life of its people throughout the 20th century.

The trade of Lace.

By the end of the 19th century, the people of

Lefkara had realised that their lace and embroideries which for centuries had been made by Lefkara women could be sold abroad at very good prices. Merchants thus began to travel abroad, first to Egypt, in particular to Alexandria, where at that time, a flourishing Greek community existed. From there, they began travelling on to Smyrna and Constantinople, where again there were thriving Greek populations. Encouraged by their success in selling lace, some of these young merchants decided to travel to Europe, once they had been given addresses of contacts. Not only did the lace trade have an important impact on both the economic and social life of the people of Lefkara but it also influenced their attitudes. These young Lefkara men who took the initiative and travelled to Europe, knowing but a few words in foreign languages, withstood the difficulties and dangers associated with travel in those times, and were well rewarded financially for their enterprise. While living in Europe they not only managed to learn to communicate in most European languages but were also influenced by the cultures of the various countries they visited. They brought home goods and equipment for everyday use but, more significantly, they, also, brought back new ideas.

Lefkara lace as art.

According to some experts, the Lefkara lace made during the period 1910-1930 reached a zenith in terms of both art and perfection, and is considered to be one of the finest examples of the craft in the modern world.

Careful examination of a lace tablecloth will

reveal a plethora of intricate figures and designs and each individual design has been given a name related to flora of the village.

Girls and women of all ages work at the fine stitching from morning to late afternoon either sitting outside their front doors in summer or inside their picturesque houses in winter and by this means the tradition is preserved. Tens of thousands of tourists visit Lefkara every year to witness this craft with their own eyes and buy some lace as presents for their families and friends.

However it is not the only example of excellence in craftsmanship in the village and silversmiths have successfully practiced their skills since the 19th century.

The architecture - Monuments and museums.

The architecture of Lefkara's houses with their enclosed gardens and balconies, as well as the village's narrow cobbled streets covered with arches create interesting features.

The church of the Holy Cross is an attractive monument dating back to 14th century with a wooden engraved iconostasis of rare beauty. The House of Patsalos, which became the Folk Museum of Lefkara contains excellent examples of the lace and embroidery craft some dating back to 19th century. The very same house is a splendid example of 19th century architecture which typifies the village. ■

