

# Newsletter 18

## Contents

Welcome note.  
Remedica worldwide.  
Our Products.  
Health matters.  
Environmental Issues.

Corporate Social Responsibility.  
The ABC of Pharmacy.  
Remedica news.  
Remedica people.  
A glimpse of Cyprus.

## Welcome note

Welcome to the 18<sup>th</sup> issue of our Newsletter in which we present our associates in Serbia, our in-house physician Dr. Kannavas and our product Kapetral® (Capecitabine). We define the term “granulation”, and discuss the issue of colon cancer. In our Environmental Issues section we present the problem of air-borne emissions. In our Corporate Social Responsibility section we report on Remedica's efforts to promote education and health in Cyprus by offering a prize to the top graduate of a local college, its participation in a Dragon Boat charity race, internal awareness campaigns on the occasion of World Environment Day and World Blood Donors Day and lots more. In Our News we describe Remedica's participation in the conferences “Health and Pharmaceutical Policies Forum - Roadmap to 2020” and the “Joint Cyprus - Greece Dermatology & VD Conference 2012” but also report Dr. Kannava's retirement. Finally, we take a glimpse at the provincial town of Paralimni.



Charalambos Pattihis,  
Group Managing Director

## Remedica Worldwide: Alvogen Pharma, Serbia



Recent developments in the legal framework in Serbia favour products that are manufactured locally as opposed to imports, so Remedica has decided to assign the rights to distribute all of its products to Alvogen Pharma Serbia together with all other necessary authorisations. Alvogen Pharma Serbia belongs to the Alvogen Group, a global generics manufacturer and supplier which has its headquarters in Parsippany, New Jersey, USA and offices in 20 countries.

Alvogen has recently constructed a packaging facility in Barice, Opština Plandište, Vršac, Serbia and obtained the necessary approvals from the relevant authorities. The primary and secondary packaging facility has been operational since November 2011, less than a one year from beginning of construction on the site! The packaging of Remedica's at this site will qualify them for inclusion in the reimbursement list of the Serbian Health Fund giving the company a competitive advantage.

This mutual cooperation will allow patients in Serbia to benefit from Remedica's high quality products in the treatment of a range of diseases. The collaboration between the two companies will be mutually beneficial in that for Remedica it will increase its strength in the West Balkans due to the proven track record of Alvogen in that market whereas the latter company will be able to sell high quality branded and generic products.

Alvogen's leadership team is dedicated to fostering a dynamic change-driven culture committed to meeting customer needs. The organisational structure is lean and flexible, enabling quick and effective decision making so that it can respond quickly to meet new market needs and forces. Alvogen's structure is designed to draw on local market know-how, foster customer relations and enhance local capacity to serve each market efficiently and effectively. Business Unit leaders and Country managers are charged with expanding and improving the business activities under their control.

Serbia has a well-developed domestic pharmaceutical industry and around 90% of domestic medicines is in the hands of the larger companies most of whom are privately-owned. However, foreign manufacturers are slowly increasing their presence in the country.

The prices of medicines are regulated by the government via a reference system and the reimbursement fund. State-owned pharmacies have the exclusive right to work with the reimbursement fund. Only one state-owned reimbursement fund exists.

Following a contraction of the Serbian economy in 2009, the recovery which started in 2010 has continued into 2011. GDP is now projected to increase by an average 4.6% per annum between 2012 and 2016. The high level of inflation which was estimated to be 7.3% in 2011, due to increases in excise duties and the price of oil, is expected to fall.

Health expenditure will continue to grow in line with the expansion of the economy. In terms of the percentage of GDP spent on health, Serbia has the highest level of healthcare expenditure in the region. Most health spending is in the public sector, channelled through the obligatory health insurance system. However, private sector expenditure is growing and accounted for an estimated 40% of the total expenditure and was worth US\$ 1.0 billion in 2011.

In Serbia and the West Balkan region Alvogen has following strengths:

- 1) Established representative offices;
- 2) Professionally trained teams of workers;
- 3) Established distribution channels and has significant experience in pharmaceutical marketing.

The fast introduction new branded prescription drugs and good quality generic products are key factors in Alvogen's development strategy.

A strategic development of the company image and brand on the market is necessary and will significantly increase the loyalty to its products and to the company itself. The aim is to build the branding strategy, innovative pricing policy and high quality of the products (modern and based on the individual need of the customers). ■



## Our Products: Kapetral®

Remedica Ltd. has recently developed the product Kapetral® Tablets which contains the active ingredient Capecitabine.

Kapetral® is indicated for:

- (a) the adjuvant treatment of patients following surgery of stage III (Dukes' stage C) colon cancer.
- (b) the treatment of metastatic colorectal cancer.
- (c) first-line treatment of advanced gastric cancer in combination with a platinum-based regimen.

Kapetral® in combination with docetaxel is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of cytotoxic chemotherapy. Kapetral® is also indicated as monotherapy for the treatment of patients with locally advanced or metastatic breast cancer after failure of a taxane and an anthracycline containing chemotherapy regimen or for whom further anthracycline therapy is not indicated.

Capecitabine is a non-cytotoxic fluoropyrimidine carbamate, which functions as an orally administered precursor of the cytotoxic moiety 5-fluorouracil (5-FU) and is activated via several enzymatic steps. The enzyme involved in the final conversion to 5-FU, thymidine phosphorylase (ThyPase), is not only found in tumour tissue but also in normal tissue, albeit usually at lower levels<sup>(1)</sup>.

Preclinical data has revealed that Capecitabine is preferentially activated to 5-FU in malignancies as a result of the unique localisation of the enzyme cascade and generates higher tumoral 5-FU exposure with an improved safety margin. Further results also provided evidence of improved anti-tumour efficacy and suitability for tumour-profiling therapy. It can also be used in combination with other chemotherapeutic agents and has the advantage that it can be administered orally and only needs to be taken once a day<sup>(2)</sup>.

Both normal and tumor cells metabolise 5-FU to 5-fluoro-2-deoxyuridine monophosphate

(FdUMP) and 5-fluorouridine triphosphate (FUTP). These metabolites cause cell injury by two different mechanisms. Firstly FdUMP and the folate cofactor, N5-10-methylenetetrahydrofolate, bind to thymidylate synthase (TS) to form a covalently bound ternary complex. This binding inhibits the formation of thymidylate from 2'-deoxyuridylate. Thymidylate is the necessary precursor of thymidine triphosphate, which is essential for the synthesis of DNA, so that a deficiency of this compound can inhibit cell division. Secondly nuclear transcriptional enzymes can mistakenly incorporate FUTP in place of uridine triphosphate (UTP) during the synthesis of RNA. This metabolic error can interfere with RNA processing and therefore protein synthesis<sup>(3)</sup>.

Kapetral® is available in 150mg and 500mg tablets. ■

### References:

<sup>(1)</sup> Xeloda SPC 2010

<sup>(2)</sup> Pentheroudakis and Twelves 2002

<sup>(3)</sup> Saif 2009

# Health Matters:

## Colon Cancer

Colon cancer is initiated cells in the large intestine or rectum start to grow in an uncontrolled manor. Most colon cancers originate from small, noncancerous (benign) tumors called adenomatous polyps that form on the inner walls of the large intestine and gradually develop into cancers. Although it is one of the main types of cancer-related deaths a complete cure can be achieved if it is diagnosed in sufficient time.

### Causes

- Colon cancer usually derives from precancerous polyps that exist in the large intestine.
- Genes - the DNA type: Cells can experience uncontrolled growth if there are damages or mutations to DNA, and therefore, damage to the genes involved in cell division. Cancer occurs when a cell's gene mutations make the cell unable to correct DNA damage and unable to commit suicide.
- Genes - the family type: Cancer can be the result of a genetic predisposition that is inherited from family members. About 20% of colon cancers are thought to be caused by inherited gene mutations.

### Risk Factors

- Age. About 90 percent of people diagnosed with colon cancer are older than 50.
- Race. African-Americans have a greater risk of colon cancer than do people of other races.
- A personal history of colorectal cancer or polyps.
- Inflammatory intestinal conditions: chronic inflammatory diseases of the colon, such as ulcerative colitis and Crohn's disease can increase your risk of colon cancer.
- Family history of colon cancer and colon polyps
- Low-fibre, high-fat diet.
- A sedentary lifestyle. If you are inactive, you are more likely to develop colon cancer.
- Smoking cigarettes and drinking alcohol can also increase the risk of developing colon cancer.
- Diabetes.
- Obesity.
- Radiation therapy for cancer. Radiation therapy directed at the abdomen to treat previous cancers may increase the risk of colon cancer.

### Symptoms

Colon cancer may not present with any symptoms but depending upon where the cancer is located, the sites to which it may have spread, and how big any tumour is, the following symptoms may suggest that it has developed:-

- Diarrhoea or constipation
- Changes in stool consistency
- Rectal bleeding or blood in the stool
- Pain, cramps, or wind in the abdomen
- Painful bowel movements
- Continual urges to defecate
- Weakness or fatigue
- Unexplained weight loss
- Irritable Bowel Syndrome (IBS)
- Iron deficiency (anaemia)

### Diagnosis

In order to diagnose colon cancer, physicians will carry out a complete physical examination as well as taking personal and family medical histories. Diagnoses are usually made after the physician has performed a colonoscopy (or sometimes a sigmoidoscopy) or a barium enema x-ray. A colonoscopy is a procedure where a long, flexible tube with a camera on the tip is inserted via the rectum to inspect the inside of the colon. A biopsy of any suspect tissue will be carried out and if a positive diagnosis of colon cancer is made, doctors will

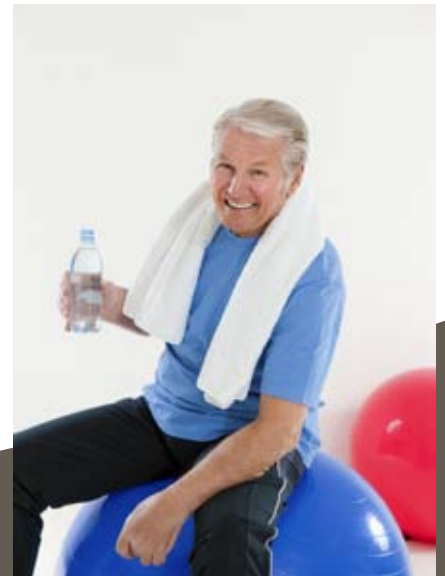
often order chest x-ray, ultrasound or CT scans of the lungs, liver, and abdomen to see how if and how far the cancer has spread. A blood test for CEA (carcinoembryonic antigen), a substance produced by some cancer cells, will often also be carried out.

### Stages of colon cancer

- Stage 0. Only signs of cancer on the surface of the epithelium.
- Stage I. Cancer has grown through the superficial lining (mucosa) of the colon or rectum but has not spread beyond the colon wall or rectum.
- Stage II. Cancer has grown into or through the wall of the colon or rectum but has not spread to nearby lymph nodes.
- Stage III. Cancer has invaded nearby lymph nodes but is not yet affecting other parts of the body.
- Stage IV. Cancer has spread to distant sites, such other organs as the liver or lung.

### Treatment

- Surgery to remove part of or the entire colon is called colectomy. During colectomy, a surgeon will remove the part of the colon containing the cancer as well as the surrounding area close to the cancer. In addition, nearby lymph nodes are also usually removed.



-Chemotherapy utilizes chemicals that interfere with the cell division process (damaging proteins or DNA) so that cancer cells will commit suicide. These treatments target any rapidly dividing cells (not necessarily just cancer cells), but normal cells can usually recover from any chemical-induced damage whilst cancer cells cannot.

-Radiation treatment, also known as radiotherapy, destroys cancer by focusing high-energy rays on the cancer cells. This causes damage to the molecules that make up the cancer cells and leads them to commit suicide.

### Prevention

Regular screening - especially after age 50 - is one of the best ways of detecting and, therefore, preventing colon cancer. Many authorities such as the American Cancer Society suggest screening by means of faecal occult blood tests (annually), stool DNA testing, flexible sigmoidoscopy (every 5 years), colonoscopy (every 10 years), and CT colonography (every 5 years).

In general, physicians recommend people to maintain a healthy weight, take regular exercise, increase consumption of fruits and vegetables and decrease their intake of saturated fat and red meat. In addition, people are recommended to limit alcohol consumption and to stop smoking. ■





# Environmental Issues:

## Air Pollution

Air pollution is defined as the introduction of chemical gases or particulates into the atmosphere which has the potential to cause harmful effects on both human health and the natural and built environment. Air pollution's effects have appeared since the dawn of the Industrial Revolution where major cities and industrial areas where burning coal in order to satisfy the need for heat and energy. Although many severe air pollution incidents have been recorded since this time, the Great Smog of 1952 in London provided the impetus for the introduction of air pollution legislation and controls in the United Kingdom.

The Great Smog was caused by the combination of airborne emissions resulting from the burning of coal and a phenomenon called temperature inversion, where a warm inversion layer of air keeps the colder air trapped below. In London in 1952 air pollutants were kept at ground level for five days claiming the lives of about 4,000 people and adversely affecting the health of a further 100,000.

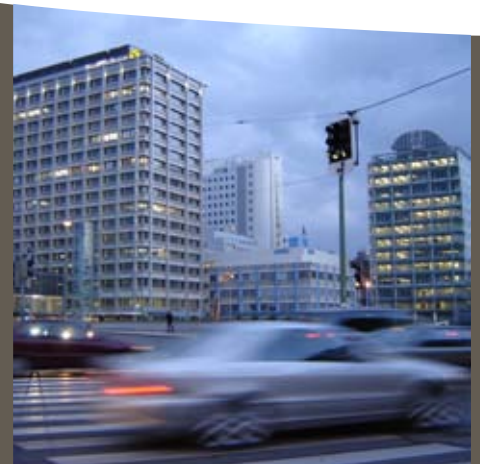
Since then many improvements have been made, yet according to the European Environment Agency a considerable number of Europeans still live in cities where air quality safety limits are constantly being exceeded. The most widespread air pollutants include particulate matter, carbon monoxide, nitrogen and sulphur oxides, volatile organic compounds and ozone. It should be noted that, although stratospheric ozone acts as a natural shield from the sun's ultraviolet radiation, it still is very toxic for life on earth it migrates to lower altitudes (troposphere). Moreover it should be noted that ozone found in the troposphere is a secondary pollutant due to the fact that it is created from reactions between primary pollutants. This is especially the case when nitrogen oxides react with volatile organic carbons in the presence of sunlight.

Sources of primary pollutants include the use of road vehicles, trains, ships and industrial processes which require the combustion of carbon based fuels. Volatile organic compounds are mainly stem from gas stations and industrial processes which require the use of solvents.

Air pollution is threatening to human health mainly due to its adverse impact on the respiratory system which may be acute, chronic or even carcinogenic. Chronic respiratory diseases are usually the result of long term exposure to pollutants and can lead to damage to the immune system and a reduction of life expectancy. It should be noted that acute effects, although rare, can cause death, usually to individuals who are already suffering from respiratory or heart diseases. Furthermore carcinogenic effects are caused mainly due to continuous exposure to hazardous volatile organic compounds.

In addition, air pollution is capable of causing adverse effects on animals and plants via their respiratory systems. According to Wright and Nebel, experiments have shown that plants are much more vulnerable to air pollutants than humans so that forests and food crops are also threatened. Furthermore, the built environment is also under threat, especially as a result of acid deposition which is caused by the presence of pollutants in the atmosphere.

Taking the above into consideration, the European Union has developed policies and legislation in an attempt to reduce air pollution. According to the European Environment Agency, the given policies and measures focus on the assessment of air emission trends and tradeoffs in different sectors, and to the availability of data for the public. ■



# Corporate Social Responsibility: Remedica Cares

## 1. Remedica's social contribution and efforts to promote education and health in Cyprus. (photo 1)

During the graduation ceremony of KES College for the academic year 2011-2012, the top-ranking graduate on the Medical Representative course was presented by Remedica's Marketing Manager, Andreas Hadjipanayis, with the Remedica monetary prize and a symbolic silver-plated olive tree. As part of Remedica's social contribution and efforts to promote education and health in Cyprus, the company offers a prize to the graduate on the Medical Representative's course obtaining the highest marks. Purely by coincidence, the top-ranking graduate Mrs. Maria Perikleous happens to be an employee of Remedica's local sales team.



## 2. Dragon Boat Charity Race. (photo 2)

Remedica took part in this charity race with its own team of 30 employees. Despite finishing the race in 4<sup>th</sup> position, all members worked as a team in a synchronised and efficient manner. All the proceeds went to the Leukemia Association "ZOE" (Life). Each Dragon Boat had on board a drummer and up to 20 paddlers. The basic aim is to build up the required speed based on synchronised paddling by all members using the proper technique.



## 3. World Environment Day: Internal Awareness Campaign. (photo 3)

In recognition of the World Environment Day, Remedica held an internal awareness campaign led by its Environmental Officer. Amongst other things, colleagues had the opportunity to be informed about the environmental problems faced by the communities we live in today and also about various good practices used by Remedica to reduce the impact of such problems.



## 4. World Blood Donors Day: Internal Awareness Campaign. (photo 4)

Remedica took the opportunity of World Blood Donors Day to organise an internal campaign aimed at encouraging colleagues to become volunteer blood donors. In addition, the company's management honoured employees who have made the greatest contribution to Remedica's blood donations. The three colleagues are Stella Alecou, George Alexandrou and Andreas Georgiou, and we wholeheartedly congratulate them yet again for their selfless contribution towards suffering fellow human beings.



## 5. Honorary Award to Remedica by the Cyprus Red Cross. (photo 5)

Remedica was presented with an honorary award by the Cyprus Red Cross for its sponsorship and support of two charity concerts given by well-known performers, Alkisti Protopsalti and Evanthis Remboutsika in aid of the children's infirmary of the Cyprus Red Cross. ■



# The ABC of Pharmacy:

## Granulation



Most medicines are manufactured as solid dosage forms such as tablets or capsules and the drug is usually a powder which has to be mixed with other ingredients (sometimes up to five or six) so that the final product can be made. In the pharmaceutical industry granulation is the procedure where the primary powder particles of the Active Pharmaceutical Ingredient (API) and a number of different excipients form larger particles which are known as “granules” (Aulton, 2007). Granules are formed by creating bonds between these particles either by compaction (dry granulation) or with the help of a binding agent (wet granulation) (Tousey, 2002).

Granules are produced for one or more of the following reasons:

- To avoid segregation (demixing) which can occur due to differences in the particle size of the API and the excipients. Segregation can occur in the hopper of a capsule filling or tablet machine, where the smaller particles tend to gravitate towards the bottom of the hopper while the larger particles become concentrated above them. This can result in an uneven distribution of the API between individual tablets or capsules: this could mean that each one might contain a different dose of the drug (Aulton, 2007).
- To improve the flow properties of the powder mixture. It is important to have a consistent particle size distribution within the mixture in order to achieve good flow properties which will prevent weight variations occurring during the compression of tablets or filling of capsules (Aulton, 2007)(Tousey, 2002).
- To improve compressibility. Most APIs are difficult to compress on their own. The presence of other excipients in the formulation improves the ability of powders to mix together and be compacted (Tousey, 2002).



### **DRY GRANULATION.**

#### **Roller Compaction.**

During the process of roller compaction, the powder mixture is squeezed between two rollers. These rollers rotate in opposite directions so that they are revolving towards each other when they meet so that they squeeze the powder mixture being fed between them which breaks into flakes under the crushing force. Granules of the desired size are then obtained by sieving (Lachman, 1986).

### **WET GRANULATION.**

#### **High Shear Mixer (HSM).**

The HSM consists of a stainless steel bowl with a stirrer at the bottom which revolves horizontally and a chopper at the side of the bowl which revolves vertically. The granulating liquid is a volatile solvent which is eventually removed during the drying of granules (water, ethanol and isopropyl alcohol are the most commonly used solvents, either separately or in combination). In most cases a binding agent (“pharmaceutical glue”) is dissolved in the granulating liquid. Povidone (PVP) is the most frequently used binder and its use will ensure that the bonds between the particles are strong once the granules have been dried (Tousey, 2002; Lachman, 1986). Most often the granules are sieve before they are dried usually in a Fluid Bed Dryer (FBD). In an FBD the hot air which is pumped from the bottom of the drier, induces the granules to fluidize which achieves homogeneous drying. After drying, the granules are sieve in order to break up particles that are too large.

#### **Fluid Bed Dryer (FBD).**

Granules can also be formed in an FBD. When the powder has become fluidized in the chamber of the drier granulating fluid is sprayed into the top and as it meets the powder particles they aggregate and then become stuck together as the solvent evaporates. As before, sieving produces the appropriate size granule. ■





# Remedica News

## 1. Participation in the conference “Health and Pharmaceutical Policies Forum - Roadmap to 2020”.

Remedica took part in the above-mentioned conference held under the auspices of the Cyprus Presidency of the Council of the European Union in 2012 and with the support and close collaboration of the Cyprus Ministry of Health.

## 2. Remedica participates in the joint Cyprus - Greece Dermatology & VD Conference 2012.

Remedica's local sales team attended two conferences where participants (doctors and other health care professional) were informed about new and existing company products. The two conferences were the Pan-Cyprian Dentistry Conference and the Cyprus-Greece Dermatology and Venereal Diseases Conference 2012.

## 3. Honorary plaque by the charity organisation “ZOE”. (photo 1)

At a charity dinner organised at her house by Remedica's Head of Analytical Development Mrs. Maria Kallidou in aid of the charity organisation “ZOE”, an honorary plaque was presented to the Chairman of Board of Directors of the Group, as a token of appreciation for Remedica's support towards the work of this charity.

## 4. Dr. Ioannis Kannavas retires. (photo 2)

After 9 years of cooperation with Remedica, as company doctor who was also responsible for pharmacovigilance issues, Dr. Ioannis Kannavas decided to retire. In his honour, a small ceremony was held where he was also presented with a silver-plated olive sapling as a token in respect of his contribution to the Company. ■



# Remedica People

In this edition we present Dr. Ioannis Kannavas who has recently retired from his post as company physician.

In this edition we present Dr. Ioannis Kannavas who has recently retired from his post as company physician.

He began his studies in the Medical School of the University of Athens from which he graduated in 1968 with a degree in medicine and became registered as a doctor. Until 1972 he worked as a general surgeon in the Municipal Hospital of Athens and from 1972 to 1979 as a specialist surgeon at Limassol General Hospital. In 1979 he formed his own private practice, which he ran until 2003. Dr. Kannavas was one of the first surgeons to use the laparoscopic surgical techniques after due training by Professor Frantzides in Wisconsin.

As an active member of both the Cyprus and the Limassol Medical Associations, he took part in many events and scientific conferences. His great love of sports led him to become

actively involved in the Supreme Council of Athletes' Health of the Cyprus Sports Association and in the Cyprus Association of Sports Medicine. He took part in many overseas tours by the Cyprus national football team and was for many years medical officer at the Tsirion Stadium in Limassol.

During the period 2001 – 2003 he was a Member of the Drugs Council of the Cyprus Ministry of Health. From 2003 until 2012 he provided medical cover for Remedica whilst also assuming responsibility for the medical aspects of Remedica's pharmacovigilance activities.

He is married to Demetra and with who he has had two children, Christoforos who is a surgeon at Limassol General Hospital, and Maria who is a lawyer. ■



# A glimpse of Cyprus: Paralimni

Paralimni is located in the south-eastern part of Cyprus and took its name from a seasonal lake which forms west of the community, between Paralimni and Sotira. This area is the lowest in the region and it is a natural hollow collecting rainwater from all parts of Paralimni and the neighbouring hills. Thus, every winter this rainwater forms a lake which lasts until the summer.

Paralimni has not always been situated in its current position. Originally it was built on a hill between Deryneia and its present location. However, in the 16<sup>th</sup> century, it was moved inland in an attempt to avoid detection by the sea pirates. It is said that the first people to settle at Paralimni arrived just after the capture of the nearby town of Famagusta by the Ottoman Turks in 1571. The first settlement was called after Saint Demetrius and to this day it still bears his name.

Paralimni became a municipality in 1986, the largest in the free Famagusta District with 15,000 inhabitants. It is the capital of the district and will remain so until the day Famagusta will be free to take back its role. The civil council consists of the Mayor and 10 Councillors all of whom are elected every 5 years.

This area was, and still is, the most productive region of Cyprus. Hundreds of windmills there testify to the productivity of the past half century whilst affording quaint, nostalgic as well as tranquil beauty to the landscape of today.

A modern road network connects Paralimni with the other areas of Cyprus, and its visitors have the chance to travel easily all over the unoccupied area.

Since the occupation of Famagusta by Turks in 1974, Paralimni has been the centre of the social, cultural and economic life of the district. The community therefore has a rich cultural tradition and combines the pleasures of a traditional village with the advantages of a modern city. During the summer cultural events are held in the squares and streets of Protaras and in the amphitheatre in Paralimni, whilst during the winter these are to be found in the town hall and the city's main square.

The tourist area of Paralimni extending along its eastern coast is one of the loveliest areas of Cyprus. For example Protaras is the name given to a picturesque bay surrounded by crystal-clear waters and golden sand with a small island about 100 meters from the beach. The bay is referred by visitors as the Fig Tree

Bay. In recent years, due to its rapid development, the whole tourist area of Paralimni Municipality has been referred to as Protaras and it now extends for approximately 10 kilometers beginning in the north in the Kapparis locality and ending in the south at Konnos.

Other areas along this coast are the Ayia Triada Bay, Vrysouthkia Bay, Pernera, Vrissi Beach, the Islands Bay and numerous others.

Not surprisingly, Protaras is a very popular holiday resort for local and foreign visitors. It is ideal for family vacations and has about 20000 hotel beds. The area (Protaras and Ayia Napa) contributes about 40% to the total of the country's income from tourism.

If you are looking for a holiday which will appeal to those of all ages and tastes, then Protaras has a lot to offer with its spectacular natural beauty, clear blue water, sheltered coves, a crystal clear seabed, rich underwater marine life and the most popular beaches on the island. ■

References: Paralimni Municipality

