

Newsletter 20

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Welcome note



Dear friends and associates,

Welcome to the 20th issue of our Newsletter through which I would like to communicate the below message:

Lately, due to the sad and unprecedented economic developments our small island of Cyprus, a member of the European Union, has found itself as a focus of attention in worldwide news.

In order to demonstrate our responsibility towards our human resource, our worldwide agents, suppliers, other associates and, most importantly, our patients, as Group Managing Director of Remedica, I would like to assure you of the following:

Our organisation with its 53-year history, based in Cyprus and exporting products to over

100 countries worldwide, is operating (and will continue to operate) like before whilst intensifying our efforts to grow the Company which, in turn, will ensure the availability of medicines to fulfill the needs of the patients. It was inevitable that the unfortunate decisions of the Eurogroup and the associated financial crisis would create difficulties for our Company: what is uncertain is their nature and extent.

However, all the agreements with our associates will continue to be honoured to the full and orders from the various countries we do business in are being fulfilled as normal. Indeed, we have won many international tenders by offering competitive prices and prompt delivery and the continuance of this policy will enable us, not only keep our work force but also to ensure Remedica's future with all the associated benefits to other stakeholders. In addition, pharmaceutical production in all of our 5 factories continues as normal and by way of further proof of our commitment, we may well have been the only company in Cyprus who paid staff their full salary at the end of March.

As the head of one of the largest Cypriot-owned organisations and one of the

biggest employers in Cyprus, you may rest assured that I will work with my colleagues so that Remedica will grow even more, creating in the process, additional work places through our business activities and thereby bring additional income to Cyprus.

Furthermore, Remedica's personnel will continue to work with continued zeal for the benefit of patients and healthcare professionals and will go on developing treatments for a healthier world.

Should any of our customers and colleagues feel that we are not performing to our past level, then I would be grateful if they would contact us at the earliest opportunity so that we can resolve any issues, however small.

I would like to take this opportunity to highlight the following advantages that Remedica has to offer:

- Knowledge, experience and professionalism since 1960.
- Strategic co-operations and alliances with international partners and companies.
- Commercial and technical expertise in our field.
- Business culture based on mutual respect and transparency.
- Dedicated and experienced

personnel.

- Strategic geographic location at the cross-roads of Europe, Asia and Africa as well as being a member of the European Union.

- 5 state-of-the-art factories approved by international competent authorities to operate under current Good Manufacturing Practices (cGMP).

- Newly-completed factory for the production of oncology products.

- Family-run business which can react quickly and effectively to outside events.

Finally I would like to emphasise not only the entrepreneurial qualities of the Cypriot nation but also their maturity, responsibility and determined attitude which lead us to believe that Cyprus will soon be in a much better position. In order to sustain these natural characteristics through these difficult times, it falls to all of us to support Cyprus businesses and products, since, in so doing, we will contribute to the future of the country by the creation of new jobs and wealth.

Yours sincerely and with my best wishes for the future

Charalambos Pattihis

Group Managing Director, Remedica. ■

Our Products: Imarem[®] (Imatinib)

The treatment of chronic myeloid leukaemia (CML) drastically changed with the introduction of imatinib, a Bcr-Abl tyrosine kinase inhibitor (TKI), in 1998. By directly targeting this leukemogenic protein kinase, imatinib produces sustained chromosomal remissions in patients with CML, which translate into prolonged survival¹.

More specifically, Imatinib is indicated for:

- paediatric patients with newly diagnosed Philadelphia chromosome (bcr-abl) positive (Ph+) chronic myeloid leukaemia (CML) for whom bone marrow transplantation is not considered as the first line of treatment;
- paediatric patients with Ph+ CML in chronic phase after failure of interferon alfa therapy,

or in accelerated phase;

- adult and paediatric patients with Ph+ CML in blast crisis.

The effect of imatinib on the outcome of bone marrow transplantation has not been determined.

In adult and paediatric patients, the effectiveness of imatinib is based on overall haematological and cytogenetic response rates and progression-free survival in CML. Except in newly diagnosed chronic phase CML, there are no controlled trials demonstrating a clinical benefit or increased survival for these diseases².

Imatinib is a potent inhibitor of three tyrosine kinases:

- Ablason (ABL),
- Platelet derived growth-factor receptor (PDGFR) α and β ,
- KIT

These tyrosine kinases play a significant role in the growth and proliferation of malignant cells in CML, GIST (gastro-intestinal stromal tumours) and the rare disease dermatofibrosarcoma protuberans³.

Imatinib exerts its therapeutic effect in CML through competitive inhibition of the ATP (adenosine triphosphate) binding site of Bcr-Abl tyrosine kinase, thereby inhibiting tyrosine phosphorylation of proteins involved in Bcr-Abl signal transduction⁴.

At the clinical level, this translates into selective inhibition of proliferation and

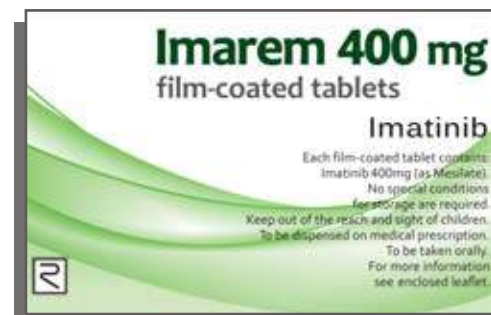
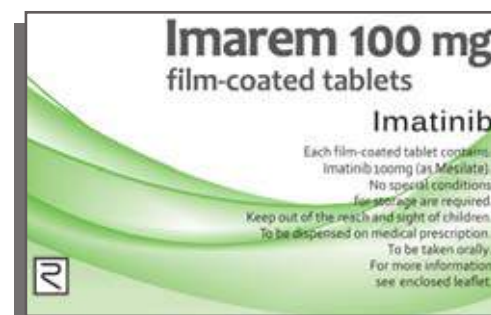
induction of apoptosis in Bcr-Abl-positive cells, with no effect on normal cells⁵.

During the IRIS study, the efficacy of imatinib was compared with that of IFN alfa (interferon alfa) combined with low-dose cytarabine in newly diagnosed chronic phase (CP) CML. Patients were evaluated for haematologic and cytogenic responses (CRs), toxic effects and rates of progression.

The authors concluded that in terms of haematologic and CRs, tolerability and the likelihood of progression to accelerated phase or blast crisis CML, imatinib was superior to INF alfa plus low-dose cytarabine as first-line therapy in newly diagnosed CP CML⁶.

Remedica Ltd. has developed imatinib tablets under the trade name Imarem.

Imarem tablets are film-coated tablets



containing either 100mg or 400mg of imatinib (as mesylate). ■

References:

- ⁽¹⁾ Agrawal et al 2010
- ⁽²⁾ Glivec SmPC
- ⁽³⁾ De Kogel and Schellens 2007
- ⁽⁴⁾ Druker et al 2001a
- ⁽⁵⁾ Druker et al 1996 and 2001a, Deininger et al 1997, Gambacorti-Passerini et al 1997
- ⁽⁶⁾ O'Brien et al 2003b, O'Brien and Deininger 2003

The ABC of Pharmacy:

Tabletting

Tablets are made by compressing a powder mixture which consists of the Active Pharmaceutical Ingredient (API) and a number of other ingredients (excipients) on machines called 'tablet presses'.

A tablet press consists of the following main components^{1,2}:

- The hopper where the powder mixture is placed prior to being compressed.
- The dies, which can be round, oval or capsule shaped depending on the shape of the tablet it is intended to produce.
- The punches (upper and lower) which are used to compress the powder mixture within the dies and form the tablet.
- A feed frame which guides the powder mixture from the hopper to the dies in order to be compressed.

There are two types of tablet presses, the single punch press and the rotary press. As the name suggests, a single punch press consists of only one die and only one set of punches. On the other hand a rotary press may have from about 4 punches on development scale machines to as many as 60 or more on large production machines¹.

The powder mixture is placed in the hopper of the tablet press. The process followed to produce tablets can be split into three stages which are also known as the "compaction cycle"². During the first stage of this cycle, the die is filled with the powder from the hopper while its lower end is closed by the lower punch.

During the second stage the upper punch descends and compresses the powder inside the die until a tablet is formed which is dependent upon the compression force having been set to the correct level for the particular product. After the tablet has been formed the upper punch ascends from the die. During the last stage of the compaction cycle the lower punch rises until it reaches the top edge of the die and the tablet is pushed towards a collecting vessel.².

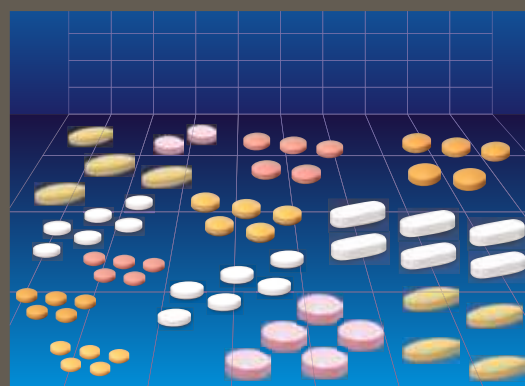
A lubricant must be included in all formulations since it reduces friction between the powder mixture and the die wall and also promotes flow of the powder mix. Not reducing this friction can result in problems during the compression process, for example, sticking of powder to the punches can mean that tablets are either not formed or, if they are, they are unsatisfactory.

During compression it is also important for the powder mixture to exhibit good flow. In cases where there is an open feeder and the feed frame is filled under the influence of gravitational force, the powder must flow freely in order to avoid weight or hardness variations in the resultant tablets. This issue can be eliminated by the use of force feeding where the powder is forced into the feed frame with the help of a specialised mechanism. ■

References

¹⁾ The theory and practice of industrial pharmacy, Lachman, 1986

²⁾ Pharmaceutics: The science of dosage form design, M.E. Aulton, 2007.





Environmental Issues: Pollution of the seas.

Pollution of the seas is defined as the introduction of solid waste, chemical substances or biological factors into the sea. Sea pollution alters the marine ecosystem and prevents the functioning of natural processes, resulting in undesired events both for its inhabitants and for human beings. It should be noted that according to the European Commission, each year millions of tons of solid waste are introduced at the world's seas, turning the global oceans into the biggest dumping site on the planet.

Although the sea is considered to be the most efficient organic digester, it nevertheless does not have the capacity to dissolve any kind of urban, rural or industrial waste. As a result, many pollutants can persist in the water causing acute and long term effects to the marine ecosystem. It could be argued that the most widely known effects of sea pollution are caused by accidental oil tanker spills.

Oil spills have a devastating impact on marine environment due to the fact that oil affects the health of microorganisms present in water, as well as fish, mammals and even sea birds. In addition, the presence of oil on the surface of the water has a long-term cumulative impact on the marine ecosystem, affecting its natural cycles.

Despite the devastating impacts of oil spills on the marine environment, it should be noted that according to the European Environment Agency, large accidental oil spills account for only 10-15 per cent of all oil that is introduced into the sea. On the contrary, as reports conducted by the same source have illustrated, the major source of pollution of the seas is caused by land-based discharges

of oil. Moreover, other chemical pollutants have as their source various rural activities. For example, runoffs from soil containing pesticides and chemical fertilisers are also a major threat to the marine environment, due to the fact that contaminated rivers and streams eventually empty into the sea. In addition, non-treated industrial waste discharged into the sea, may introduce a variety of dangerous substances such as heavy metals, phenols and grease which have the potential to cause possibly irreversible effects to the area of discharge.

Another major source of sea pollution includes the discharge of untreated municipal wastewater from urban areas or tourist premises into seawater. Municipal wastewater pollution introduces pathogens into seawater such as disease causing bacteria, viruses and other parasitic microorganisms: human beings can become infected if they bathe in contaminated waters.

In addition, the discharge of solid waste at sea as well as littering of the seawater can also cause pollution. Solid waste such as plastics, batteries and electrical and electronic devices, can release toxic substances such as heavy metals into the water which can poison living organisms.

Taking the above into consideration, the Integrated Maritime Policy and the Marine Strategy Framework Directive were adopted by the European Union in 2008. According to the European Commission the main objective of this Framework is to achieve and maintain a good environmental status of all European seas by 2020 at the latest. ■



Corporate Social Responsibility

Remedica Cares

1) Donation to municipal social groceries. (photo 1, 2)

As part of its general programme to alleviate suffering in the community, Remedica made a monetary donation which enabled the provision of food and other essential items via municipal groceries to families facing serious financial hardship in three municipalities, namely Limassol, Larnaca and Paphos.



2) Donation to the Pattichis Senior Citizens' Centre.

Once again, Remedica has sponsored this Centre which, unique in its kind in Cyprus, for 12 years has made a valuable contribution to senior citizens of Limassol. Its main aim is to provide entertainment and a variety of other services to its members so that they may become more active citizens.



3) Social activity programme promoting education. (photo 3)

In order to raise awareness of the activities of the Company in the eyes of the community, Remedica received educational visits from the pupils of St. Peter's & Paul's Lyceum, the Polemidhia Lyceum, and Foley's School. After being briefed on the Company's activities, the pupils were given a tour of the Quality Control Department where they had the opportunity to see the state of the art instrumentation and technology used by Remedica.



4) Professions in demand in the pharmaceutical industry.

In order to encourage young people to read for university degrees that are in high demand in the pharmaceutical industry, Remedica has begun an awareness campaign in schools. Two schools have already been visited and the pupils were informed about the activities of the Company and the employment opportunities that it will be able to offer in the future.

5) Donation of pharmaceuticals. (photo 4, 5)

In an attempt to improve the therapeutic treatments available to fellow human beings living under challenging conditions, Remedica dispatched a consignment of pharmaceuticals to the Gaza Strip and a Syrian refugee camp in the Lebanon. The first mission was carried out by the Cyprus Rotary Club in collaboration with the Ramallah Rotary Club and the second by the Volunteer Doctors - Cyprus. As a gesture of appreciation for the mission to Lebanon, children there painted a flag with Remedica's logo and sent it to the Company's management.

6) Honourary certificate. (photo 6)

At a recent meeting of the Famagusta Rotary Club, its President Mr. Andreas Capetanios and the representative of all the Rotary Clubs of Cyprus, Dr. George Papaleontiou, made a formal recognition of Remedica's support of the suffering Palestinian people. A Certificate of Appreciation and a copy of the publication 'Rotary Basics' was received on behalf of Remedica by the company's Marketing Manager, Andreas Hadjipanayis. ■

Health Matters:

Leukaemia.



Leukaemia (from the Ancient Greek λευκός leukos "white", and αἷμα haima "blood") is a type of cancer of the blood or bone marrow characterized by an abnormal increase of immature white blood cells called "blasts".

Leukaemia is subdivided into acute and chronic forms.

Acute Leukaemia is characterised by a rapid increase in the number of immature blood cells that prevents the bone marrow from producing healthy blood cells such as red blood cells and platelets which are required for blood to clot. Acute forms of leukaemia are the most common ones that occur in children and immediate treatment is essential.

Chronic Leukaemia is characterised by the excessive buildup of relatively mature, but still abnormal, white blood cells. Chronic forms of leukaemia are sometimes monitored for some time before treatment to ensure maximum effectiveness of therapy. Chronic leukaemia mostly occurs in adults and is rarely found in children.

Both types are further subdivided according to the type of blood cell that is affected and are known as either lymphoblastic or lymphocytic or myeloid or myelogenous leukaemias.

In lymphoblastic or **lymphocytic leukaemias**, the cancerous change takes place in a type of marrow cell that normally goes on to form lymphocytes, which are infection-fighting immune system cells.

In myeloid or **myelogenous leukaemias**, the cancerous change takes place in a type of marrow cell that normally goes on to form red blood cells, some other types of white cells, and platelets.

Both forms are subdivided into four main categories.

Acute lymphoblastic leukaemia (ALL) is the most common type of leukaemia to occur in young children although it can also affect adults, especially those aged 65 and older. The survival rates vary by age: 85% in children and 50% in adults.

Chronic lymphocytic leukaemia (CLL) most often affects adults over the age of 55. It sometimes occurs in younger adults, but it

almost never affects children. The five-year survival rate is 75%.

Acute myelogenous leukaemia (AML) occurs more commonly in adults than in children, and more commonly in men than women. The five-year survival rate is 40%.

Chronic myelogenous leukaemia (CML) occurs mainly in adults; a very small number of children may also develop this disease. The five-year survival rate is 90%.

Other subtypes of Leukaemia are:

Hairy cell leukaemia is sometimes considered a subset of chronic lymphocytic leukaemia. About 80% of those affected are adult men and no cases have been reported in children. Survival is 96% to 100% at ten years.

T-cell prolymphocytic leukaemia is a very rare and aggressive leukaemia affecting adults. It is difficult to treat, and the median survival is measured in months.

Adult T-cell Leukaemia is caused by human T-lymphotropic virus (HTLV), a virus similar to HIV. It endemic in certain areas of the world.

Signs and symptoms

Damage to the bone marrow results in a lack of blood platelets, which are important in the blood clotting process. This means people with leukaemia may easily become bruised, bleed excessively, or develop pinpoint bleeds (petechiae).

White blood cells, which are involved in fighting pathogens, may either be suppressed or dysfunctional. Because leukaemia prevents the immune system from working normally, some patients experience frequent infection, ranging from infected tonsils, sores in the mouth, or diarrhoea to life-threatening pneumonia or opportunistic infections.

Finally, the red blood cell deficiency leads to anemia, which may cause dyspnoea and pallor.

Some patients experience other symptoms, such as nausea, fevers, chills, night sweats, fatigue and other flu-like symptoms. Blasts affected by the disease may accumulate in the liver (or in the lymph nodes) which becomes swollen and as a result the patient may experience a feeling of fullness as well as losing weight unintentionally.

Causes

No causes of any kind of different types of leukaemia have been identified since, like other cancers, they result from mutations in DNA. Among adults, some causes have been identified such as natural and artificial ionizing radiations, and some viruses. Chemicals, notably benzene and alkylating chemotherapeutic agents used to treat previous malignancies are also known to initiate leukaemia. Use of tobacco is

associated with a small increase in the risk of developing acute myeloid leukaemia in adults and exposure to some petrochemicals and hair dyes may also be implicated in certain types of the disease. A few cases of maternal-foetal transmission have been reported.

Diagnosis

Complete blood counts are pivotal in diagnosis together with examination of bone marrow and lymph node biopsies. X-ray, MRI, or ultrasound may all be used to aid diagnosis of the disease in certain parts of the body.

In many cases a diagnosis will have not been made due to the vague, unspecific, nature of the symptoms which might easily lead to the diagnosis of another non life threatening disease. It has been estimated that at least one-fifth of the cases of leukaemia have never been diagnosed.

Treatment

Most forms of leukaemia can be treated with a multi-drug chemotherapy regimen (which often includes Imatinib). In some radiation therapy will be used and bone marrow transplants can also be useful. ■

Remedica News

1) Remedica's new oncology facility passes GMP inspection. (photo 1)

The company's newest facility which will be dedicated to the manufacture of oncology products recently passed an official GMP inspection by the Pharmaceutical Services Department of the Cyprus Ministry of Health and has begun operations. Remedica's oncology product range will gradually be transferred to the new facility and the existing one will serve as a back-up.

2) Visit by EU officials.

In the context of Cyprus holding the European Union Presidency, government officials and civil servants from various Member-States were given a tour of Remedica's facilities and had the opportunity to learn more about the company and see its modern laboratories.

3) Cutting the Christmas cake. (photo 2, 3, 4)

Remedica held a modest ceremony in its facilities in order to cut the Vassilopitta (Christmas cake), and the money that would have been spent on an annual staff party was donated to various municipal groceries in Cyprus. In his speech, the Managing Director of Remedica Ltd, referred to the difficult times facing Cyprus in view of the economic crisis, as our company has also been affected to some degree, and called upon all staff to contribute in their own way towards further growth.

Group Managing Directors, Mr. Charalambos Pattihis and Mrs. Andri Aristotelous (who until recently was head of the Accounts department and retired after 39 years of service) jointly cut the Vassilopitta. Remedica's staff thanked the company's management for the successful course they have been following and for crafting a growth strategy that ensures the standard of living of all concerned whilst presenting Remedica's Chairman, Mr. Chris Pattichis with a token gift on account of his name day. ■



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A glimpse of Cyprus: Troodos Mountains.

The mountainous cluster Troodos is the tallest mountain range in Cyprus with peaks that reach an altitude of 1952 metres. Troodos is also the name given to the region near the very top, namely that of Chionistra (snowy area in Greek). There the three roads that connect the mountains with Nicosia, Limassol and the village of Prodomos meet, from where name ("three roads" in Greek – "Troodos") is also derived. The mountainous area of Troodos occupies the central and south-western part of the island with a ridge that extends from West-north-west to East-south-east. Since it covers 2/3 of the island it constitutes the main geographical feature and geological trait of Cyprus.

Scientifically it is known as the Ophiolitic Cluster of Troodos having been created 80 million years ago and rising above sea level 20 million years ago thereby creating the island. It is one of the very best-researched geological phenomena in the world and has shed much light on the origins of the earth's crust.

The mountain range of Troodos is host to many forest areas and rich flora with a significant number of endemic plants. Also it plays an important role in the control of the island's water supply, as not only do many rivers rise there but it also contributes substantially to the enrichment of underground water. Due to the natural environment, the climate and the cultural heritage, Troodos constitutes an important focus of attraction for sightseers and as a place of recreation.

Administratively the mountain range of Troodos is shared between four districts, Nicosia in the North, Pafos in the West, Limassol in the South and Larnaka in the East. Countless villages are found scattered

throughout the entire mountain range, apart from the Pafos Forest in the West where there are no permanent residents. The mountain villages of Troodos are mainly located in the valleys of Marathasa and Solea in the North, in the central Pitsillia region, in the Krasochori (wine village) region of Limassol and Pafos in the South, and in parts of the Orini (mountainous) region in the East.

Even today, the region's economy is to a large extent based upon agriculture. The climate at the higher altitudes favours the cultivation of deciduous fruit trees, such as apple and cherry, that represent the basic produce of the villages of Marathasa and Pitsillia. Large areas are also dedicated to the cultivation of vines, particularly in the semi-mountainous villages of the Limassol district, which are consequently renowned for the production of wine.

The mining of minerals and metals has fallen into a decline in recent times, since the extraction of asbestos and chrome was halted in the 1980s, while copper mining is now carried out only on a limited scale in the mine at Skouriotissa situated in the Solea valley.

Logging has also ceased to play an important role in the economy of the region, as the forests of Cyprus produce relatively few trees due to the unsuitability of the climate. In the past few years, emphasis has been given to recreation activities and to the preservation of forests.

Scattered throughout the Troodos region are many churches and monasteries, which constitute outstanding monuments of Byzantine art. Typical examples are the

churches with gable roofs covered with flat, slotted tiles, a feature that prevailed in the region from the 12th century. Ten churches in the Troodos area have been included in the list of World Cultural Heritage of UNESCO with the title "Painted Churches in the Troodos Region", mainly due to the murals, that cover their interior and are considered to constitute marvellous examples of Byzantine and post-Byzantine church painting.

Thanks to the climate, the natural environment, the diversity of landscape and the cultural heritage, Troodos offers countless opportunities for exercise, recreation and tourism. In the state-owned forests of Cyprus there are 52 sign-posted paths in areas which allow nature study and these total 232.5 kilometres in length. Moreover, a large number of fully equipped camping sites are available in the vicinity.

With regard to sports, the forest offers ideal conditions for mountain cycling and the network of suitable trails is being extended. Also, during winter months in the Chionistra region, there is a ski centre with slopes for alpine and long distance skiing.

There are numerous hotels and agrotourism (agritourism) lodges in the surrounding villages, with Platres being the most prominent resort. Finally we cannot leave the mountains without mentioning that Troodos was identified as one of the 10 best upcoming agro-tourism destinations in Europe during the Forum "Top Class European Destinations" held in Lisbon in October 2007. ■

References: Wikipedia



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