

DRUG INFORMATION BULLETIN

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Drug Information Bulletin

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Editorial

These are exciting times to be learning and practising pharmacy. Development of medicines and the delivery of care are moving towards personalized therapies and pharmacogenetics. These developments bring about greater responsibility and increased opportunities for pharmacists to ensure rational and safe use of medicines. Pharmacists, together with other healthcare professionals are key players in ensuring that drugs particularly innovative drugs are safe when they reach the market, are prescribed appropriately, are used safely and are accessible to those individuals who need them. To achieve this, information about use of drugs should be disseminated to pharmacists and other healthcare professionals.

The Drug Information Bulletin aims to provide information on medicines recently released on the local market and to highlight updates to medicines characteristics.

Lilian M. Azzopardi
Head
Department of Pharmacy

Editor-in-chief

Prof. L M. Azzopardi

Executive Editor

Alison Brincat

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This bulletin is a student project undertaken in partial fulfilment for the requirements leading to the Bachelor of Pharmacy (Hons.) degree under the supervision of Professor Lilian M. Azzopardi B.Pharm.(Hons.), M.Phil., Ph.D., Head of Department of Pharmacy, University of Malta.

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Department of
Pharmacy,
University of Malta,
Msida MSD 2080
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Tel: +356 21343764/5
Fax: +356 21340427
E-mail: phcy@um.edu.mt

Contents

New medicinal products available on the local market

Aciclovir Merck	page 3	Eltroxin TM	page 6
Altargo [®]	page 3	Esmeron [®]	page 6
Amoxicillin/Acide Clavulaniqe Merck	page 3	Invega TM	page 6
Androge [®]	page 4	Losec [®] IV	page 7
Atacand Plus [®]	page 4	Lidocaine injection	page 7
Avamys [®]	page 4	Nexium [®] IV	page 7
Betaser [®]	page 4	OncoTICE [®]	page 7
Canesten [®] Oral & Cream Duo	page 4	Pregnyl [®]	page 8
Carboplataine Merck	page 5	Rinialer [®]	page 8
Concerta [®]	page 5	Suboxone [®]	page 8
Cosopt [®]	page 5	Vicombil [®]	page 8
Cozaar [®] -COMP	page 5	Wellbutrin [®] XR	page 9
Crestor [®]	page 6	Xylo-POS [®]	page 9

Variations in Summary of Product Characteristics of medicinal products available locally

Avandamet [®]	page 10	Mirapexin [®]	page 15
Avandia [®]	page 10	Mircera [®]	page 15
Avastin [®]	page 10	Neoclarityn TM	page 16
Axura [®]	page 11	Orgalutran [®]	page 16
Betaferon [®]	page 11	PegIntron TM	page 16
Caelyx [®]	page 11	Prevenar TM	page 16
CellCept [®]	page 11	Prezista TM	page 17
Champix [®]	page 12	Protelos [®]	page 17
Cialis [®]	page 12	Rapamune [®]	page 17
Ferriprox [®]	page 12	Rebetol [®]	page 17
Forsteo [®]	page 12	Remicade [®]	page 18
Humira [®]	page 13	Rotarix [®]	page 18
Infanrix Hexa [®]	page 13	Twinrix Adult [®] /Twinrix Paediatric [®]	page 18
Intron [®] A	page 13	Velcade [®]	page 19
Invega TM	page 13	Vfend [®]	page 19
Januvia TM	page 14	Viagra [®]	page 19
Keppra [®]	page 14	Xagrid [®]	page 19
Levitra [®]	page 15	Zonegran [®]	page 20
MicardisPlus [®]	page 15		

New medicinal products available on the local market

From December 2007 till May 2008, the following new medicinal products have been included to our vast range of pharmaceutical products used locally both in the private and hospital pharmacies. They have been granted a marketing authorisation either by the centralised procedure or by the mutual recognition procedure or by the decentralised procedure. Avamys[®], Altargo[®], Suboxone[®] and Invega[™] have been granted their marketing authorisation by the centralised procedure whilst Betaserac[®], Androgel[®], Wellbutrin[®]XR, Nexium[®]IV, Rinialer[®], Vicombil[®], Cosopt[®], Cozaar[®]-COMP, Esmeron[®] and Concerta[®] have been registered via a national procedure. The other medicinal products have been registered via a simplified procedure in line with article 4(2) of the Medicines (Marketing Authorisations) Regulations in accordance with article 126(a) of Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community Code relating to medicinal products for human use, as amended by Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004.

Aciclovir Merck (Merck Generiques)

Aciclovir

Pharmaceutical Form: 250mg Powder for solution for injection

Aciclovir is a synthetic purine nucleoside analogue with an inhibitory activity against human herpes viruses. Aciclovir is indicated for the treatment and prophylaxis of *Herpes simplex* infections in immunocompromised patients and severe initial genital herpes in the non-immunocompromised, *Herpes simplex* infections in neonates and infants up to three months, treatment of *Varicella zoster* infections and herpes encephalitis. It is contraindicated in patients with known hypersensitivity to aciclovir and valaciclovir. The adverse effects include nausea and vomiting and rashes.¹

References

1. Medicines.org.uk. Electronic Medicines Compendium [online]. 2008 [cited 2008 August 14]; Available from: URL: <http://emc.medicines.org.uk/>

Altargo[®] (Glaxo Group)

Retapamulin

Pharmaceutical Form: 1%w/w ointment

It is indicated for impetigo and small infected lacerations, abrasions or sutured wounds. Retapamulin, a semi-synthetic derivative of pleuromutilin, is predominantly bacteriostatic against *S. aureus* and *S. pyogenes*. It selectively inhibits bacterial protein synthesis. It is contraindicated in cases of hypersensitivity cases to

retapamulin or the excipient. The common adverse effect is irritation at the site of application.¹

References

1. European Medicines Agency. EPARs for authorised medicinal products for human use [online]. 2008 March 28 [cited 2008 August 9]; Available from: URL: <http://www.emea.europa.eu/humandocs/Humans/EPAR/altargo/altargo.htm>

Amoxicillin/Acide Clavulanique Merck (Merck Generiques)

Amoxicillin, Clavulanic acid

Pharmaceutical Form: powder for solution for injection

Amoxicillin is indicated for bacterial infections such as pneumonia, gonorrhoea and cystitis. It is also used for *H.pylori* eradication in combination with other medicines. Amoxicillin is a semi-synthetic antibiotic, which has antibacterial activity against a broad spectrum of Gram-positive and Gram-negative microorganisms. Clavulanic acid inactivates beta-lactamase enzymes, commonly found in microorganisms resistant to penicillins and cephalosporins. It is contraindicated in patients with a history of hypersensitivity reactions to beta-lactam antibiotics. Side effects are uncommon, mainly of a mild and transitory nature. These include gastrointestinal disturbance and hypersensitivity.¹

Reference

1. U.S. National Library Medicine and National Institutes of Health. MedlinePlus[®] [online]. 2008 October 2 [cited 2008 October 2]; Available from: URL: www.nlm.nih.gov/medlineplus/druginfo/meds/a685001.html

Androge[®] (Laboratoires Besins International)

Testosterone

Pharmaceutical Form: 50mg/ 5g sachet gel

Androge[®] is a topical hormone gel which is indicated for male hypogonadism when testosterone deficiency has been confirmed. It is contraindicated in cases of known or suspected prostatic cancer or breast carcinoma and hypersensitivity. The most frequently adverse drug reactions are skin reactions at the site of application. Other common adverse drug reactions include headache, hypertension, prostatic disorder, gynaecomastia and alopecia.¹

Reference

1. Medicines Authority [online]. 2008 [cited 2008 August 12]; Available from: URL: http://www.medicinesauthority.gov.mt/products/SPC_MA562%200101_Androge%20Gel_Testosterone%2050mg%20per%205g%20sachet_Laboratoires%20Besins%20International_France_PoM_G03B_A03_16.11.06.pdf

Atacand Plus[®] (Associated Drug)

Candesartan Cilextil ; Hydrochlorothiazide

Pharmaceutical Form: 16mg/12.5mg tablets

Candesartan is an angiotensin II AT₁ receptor blocker whilst hydrochlorothiazide is a diuretic. Atacand Plus[®] is indicated for hypertension. It is contraindicated in cases of anuria and hypersensitivity to the active ingredients or excipients. Some adverse effects that can occur include headache, throat infections, back pain and dizziness.¹

Reference

1. Astrazeneca. Atacand [online]. 2008 [cited 2008 August 12]; Available from: URL: http://www.atacand.com/0_0.aspx

Avamys[®] (Glaxo Group)

Fluticasone furoate

Pharmaceutical Form: 27.5 micrograms/spray, nasal spray, suspension

Avamys[®] is indicated for the treatment of symptoms of allergic rhinitis in adults and children over 6 years. Fluticasone is a synthetic trifluorinated corticosteroid which has a potent anti-inflammatory action. It is contraindicated in hypersensitivity to the active substance or to any of its excipients. The most common adverse effects are epistaxis and nasal ulceration. The incidence of the former side effect was higher in long-term use than in short-term use (up to 6 weeks) in adults and adolescents.¹

Reference

1. European Medicines Agency. EPARs for authorised medicinal products for human use [online]. 2008 January 11 [cited 2008 August 9]; Available from: URL: <http://www.emea.europa.eu/humandocs/Humans/EPAR/avamys/avamys.htm>

Betaserc[®] (Solvay Pharmaceuticals)

Betahistine Dihydrochloride

Pharmaceutical Form: 24mg tablets

Betaserc[®] is indicated in Meniere's syndrome and symptomatic treatment of vestibular vertigo. It is only contraindicated in case of hypersensitivity but caution is advised when administered to patients with a history of peptic ulceration and patients suffering from pheochromocytoma or bronchial asthma. Administration to pregnant women is discouraged although there are no indications for harmful effects in animal testing. Mild gastric complaints have occurred in some cases which can normally be reduced by taking the dose with meals or lowering its dose. Only in rare cases, hypersensitivity reactions have been reported.¹

Reference

1. Medicines Authority [online]. 2008 [cited 2008 August 12]; Available from: URL: http://www.medicinesauthority.gov.mt/products/SPC_MA013%200503_Betaserc%20Tablet_Betahistine%20Dihydrochloride%2024mg_Solvay%20Pharmaceuticals%20B.V._Netherlands_PoM_N07CA01_07.02.08.pdf

Canesten[®] Oral & Cream Duo (Bayer)

Fluconazole, Clotrimazole

Pharmaceutical Form: 150mg capsules, cream

Its main indication is for vaginal thrush. It can also be used to treat men who are suffering from thrush on the penis. The oral treatment is to treat the vaginal thrush whilst the cream is applied to vagina or penis to relieve the external symptoms of infection. It is contraindicated in known hypersensitivity. Fluconazole should not be administered concomitantly with terfenadine or cisapride. Fluconazole and clotrimazole are a triazole and an imidazole derivative respectively. They are a potent and selective inhibitor of fungal enzymes necessary for the synthesis of ergosterol. The most common side effects of the capsule are gastrointestinal disturbances and headache whilst those of the topical application are local mild irritation immediately after application rarely.¹

Reference

1. Medicines.org.uk. Electronic Medicines Compendium [online]. 2008 [cited 2008 August 14]; Available from: URL: <http://emc.medicines.org.uk/>

Carboplatine Merck (Merck Generiques)

Carboplatin

Pharmaceutical Form: 150mg/15ml solution for infusion

Carboplatin is a platinum coordination compound, used to treat ovarian carcinoma and other cancers such as lung cancer. It is contraindicated in patients with a history of hypersensitive reactions to cisplatin or platinum containing compounds and patients with severe bone marrow depression or significant bleeding. Common side effects include thinned or brittle hair, loss of appetite or weight, stomach pain, diarrhoea, constipation, changes in taste, vision and numbness.^{1,2}

Reference

1. Carboplatin.org. Carboplatin information [online]. 2008 [cited 2008 August 12]; Available from: URL: <http://www.carboplatin.org/>
2. Drug Information Online. Carboplatin [online]. 2008 [cited 2008 August 12]; Available from: URL: <http://www.drugs.com/pro/carboplatin.html>

Concerta® (Janssen Cilag International)

Methyl phenidate hydrochloride

Pharmaceutical Form: 18mg, 36mg, 54mg prolonged release tablets

Methylphenidate is a mild central nervous system stimulant which is indicated as part of comprehensive treatment programme for Attention Deficit Hyperactivity Disorder in adolescents and children over 6 years after a very thorough assessment of severity and chronicity of the child's symptoms in relation to his/her age. Its contraindications include cases of hypersensitivity, patients with marked anxiety and tension, glaucoma, hyperthyroidism and in combination with monoamine oxidase inhibitors and also within a minimum of 14 days following its discontinuation. The most common adverse effect is headache followed by nasopharyngitis, dizziness and gastrointestinal disturbances amongst others.¹

Reference

1. Medicines.org.uk. Electronic Medicines Compendium [online]. 2008 [cited 2008 August 12]; Available from: URL: <http://emc.medicines.org.uk/>

Cosopt® (Merck Sharp & Dohme)

Dorzolamide, Timolol

Pharmaceutical form: 20mg / 5mg eye drops solution

Cosopt® is indicated in the treatment of elevated intraocular pressure in patients with open-angle glaucoma or pseudo-exfoliative glaucoma when topical beta-blocker monotherapy is not sufficient. Dorzolamide is a potent inhibitor of human carbonic anhydrase II whilst timolol is a non-selective beta-adrenergic receptor blocking agent. Each of the two components decreases elevated intraocular pressure by reducing aqueous humor secretion. The combined effect of these two agents results in additional intraocular pressure reduction when compared to either component administered alone. It is contraindicated in patients with reactive airway disease including bronchial asthma or a history of bronchial asthma or severe chronic obstructive pulmonary disease; sinus bradycardia, second or third degree atrioventricular block, overt cardiac failure, cardiogenic shock; severe renal impairment (CrCl<30ml/min) or hyperchloraemic acidosis and hypersensitivity to one or both active substances or to any of the excipients. No adverse effects specific to Cosopt® have been observed during clinical studies but they have been limited to those that were reported previously with both active ingredients. Some common adverse effects are ocular burning, stinging and taste perversion.¹

Reference

1. Medicines Authority [online]. 2008 [cited 2008 July 12]; Available from: URL: http://www.medicinesauthority.gov.mt/products/SPC_MA058%2001401_Cosopt%20Eye%20drops%20solution_Dorzolamide%20mg:%20Timolol%205mg_Merck%20Sharp%20&%20Dohme%20Ltd._United%20Kingdom_PoM_S01ED51_13.09.05.pdf

Cozaar®-COMP (Merck Sharp & Dohme)

Losartan, Hydrochlorothiazide

Pharmaceutical form: 100/12.5, 50/12.5 tablets

Losartan is an oral, specific angiotensin-II receptor antagonist whilst hydrochlorothiazide is a diuretic and antihypertensive. It is indicated for the treatment of hypertension in patients whose blood pressure is not adequately controlled on hydrochlorothiazide or losartan monotherapy. In hypertensive patients with left ventricular hypertrophy a reduced risk of stroke was demonstrated with losartan administered usually in

combination with hydrochlorothiazide. The data does not support the use of losartan for this indication in black patients. It is contraindicated in pregnancy, patients who are hypersensitive to any component of this product, in patients with anuria and in patients who are hypersensitive to other sulphonamide-derived drugs. In clinical trials with the combination tablet of losartan and hydrochlorothiazide, no adverse experiences peculiar to this combination drug have been observed. ¹

Reference

1. Medicines Authority [online]. 2008 [cited 2008 August 12]; Available from: URL: http://www.medicinesauthority.gov.mt/products/SPC_MA058%2001304_Cozaar%20Comp%20100-12.5_Film-coated%20tablets_Losartan%20100mg:%20Hydrochlorothiazide%2012.5mg_Merck%20Sharp%20&%20Dohme%20Ltd.,_United%20Kingdom_PoM_C09DA01_02.11.07.pdf

Crestor[®] (Associated Drug)

Rosuvastatin

Pharmaceutical form: 5mg, 10mg, 20mg, 40mg tablet

Crestor[®] is indicated in primary hypercholesterolemia, mixed dyslipidaemia and homozygous familial hypercholesterolaemia as an adjunct to diet. Rosuvastatin is a selective and competitive inhibitor of HMG-CoA reductase. Rosuvastatin increases the number of hepatic LDL receptors on the cell-surface, enhancing uptake and catabolism of LDL. It inhibits the hepatic synthesis of VLDL, thereby reducing the total number of VLDL and LDL particles. It is contraindicated in patients with active liver disease, pregnancy and lactation and hypersensitivity to any of its components. The adverse effects are usually mild and transient which include headache, dizziness, constipation, nausea, abdominal pain, myalgia and asthenia. As with other HMG-CoA reductase inhibitors, the incidence of adverse drug reactions tends to be dose dependent. ¹

Reference

1. Medicines.org.uk. Electronic Medicines Compendium [online]. 2008 [cited 2008 September 12]; Available from: URL: <http://emc.medicines.org.uk/>

Eltroxin[™] (Goldshield Pharmaceuticals)

Levothyroxine

Pharmaceutical form: 25mcg tablets

Eltroxin[™] is indicated in hypothyroidism, congenital hypothyroidism and juvenile myxoedema. It is

contraindicated in cases of thyrotoxicosis and hypersensitivity. The side effects usually indicate an excessive dosage which on reduction of dose or withdrawal of treatment, they would disappear. These include anginal pain, cardiac arrhythmias, insomnia, headache, cramps in skeletal muscles and palpitations. ¹

Reference

1. Medicines Authority [online]. 2008 [cited 2008 August 14]; Available from: URL: http://www.medicinesauthority.gov.mt/products/SPC_MA077%2000301_EltroxinThyroxin_Tablet_Levothyroxine%20Sodium%2050mcg_Goldshield%20Pharmaceuticals%20Ltd._United%20Kingdom_PoM_H03AA01_15.05.07.pdf

Esmeron[®] (N V Organon)

Rocuronium

Pharmaceutical form: 10mg solution for injection

Rocuronium is a fast onset, intermediate acting non-depolarising neuromuscular blocking agent. It is indicated as an adjunct to general anaesthesia to facilitate tracheal intubation during routine and rapid sequence induction, to provide skeletal muscle relaxation, during surgery. It is also indicated as an adjunct in the intensive care unit to facilitate intubation and mechanical ventilation. Esmeron[®] is contraindicated in cases of hypersensitive reactions to rocuronium or to bromide ion. The most commonly occurring adverse drug reactions include injection site pain and prolonged neuromuscular block. ¹

Reference

1. Medicines Authority [online]. 2008 [cited 2008 August 14]; Available from: URL: http://www.medicinesauthority.gov.mt/products/SPC_MA031%2000201_Esmeron%20Solution%20for%20injection_Rocuronium%20Bromide%2010mg_N.%20V.%20Organon_Netherlands_PoM_MO3AC09_18.04.06.pdf

Invega[™] (Janssen-Cilag)

Paliperidone

Pharmaceutical form: 3mg, 6mg, 9mg prolonged-release tablets

Invega[™] is indicated in the treatment of schizophrenia. It is contraindicated in hypersensitivity to paliperidone, risperidone or any of the excipients. It contains a racemic mixture of paliperidone which is a selective blocking agent of monoamine effects. Paliperidone is a centrally active dopamine Type 2 antagonist and with predominant serotonin Type 2 activity. Akathisia, extrapyramidal

disorder, headache, hypotension are amongst the most common adverse reactions. ¹

Reference

1. European Medicines Agency. EPARs for authorised medicinal products for human use [online]. 2008 May 14 [cited 2008 August 9]; Available from: URL: <http://www.emea.europa.eu/humandocs/Humans/EPAR/invega/invega.htm>

Losec® IV (Associated Drug)

Omeprazole

Pharmaceutical form: 4mg/ml powder and solvent for solution for injection

Omeprazole is a specific inhibitor of the gastric proton pump in the parietal cells in order to decrease gastric acid secretion. It is indicated as a prophylaxis of acid aspiration and as a short term therapy of reflux oesophagitis, duodenal and benign gastric ulcers in patients who are unable to take oral therapy. It is contraindicated in hypersensitivity reactions and concomitant administration with atazanavir. Common adverse effects include headache and gastrointestinal disturbances such as flatulence and abdominal pain. ¹

Reference

1. Medicines.org.uk. Electronic Medicines Compendium [online]. 2008 [cited 2008 September 12]; Available from: URL: <http://emc.medicines.org.uk/>

Lidocaine Injection (B. Braun Melsungen AG)

Lidocaine hydrochloride

Strength(s): 1%w/v, 2%w/v

Pharmaceutical form: solution for injection

Lidocaine is a local anaesthetic agent of the amide type and used for local and regional anaesthesia by inhibiting the function of excitable structures such as sensor, motor and autonomic nerve fibres. In addition, it has important effects on the cardiovascular and central nervous systems. It is contraindicated in WOLFF-PARKINSON-WHITE syndrome, sudden heart failure (acute cardiac decompensation), hypersensitivity to amide-type local anaesthetics, suspicion of hereditary tendency to malignant hyperthermia, disorders of blood coagulation, anticoagulant therapy, infections in the region of injection, uncooperative patient.

In common with other local anaesthetics, adverse reactions are rare and are usually the result of raised

plasma concentrations due to accidental intravascular injection, excessive dosage or rapid absorption from highly vascular areas or may result from a hypersensitivity, idiosyncrasy or diminished tolerance on the part of the patient. Adverse effects are usually due to inadvertent intravenous administration or overdosage.

Reference

1. Medicines.org.uk. Electronic Medicines Compendium [online]. 2008 [cited 2008 September 16]; Available from: URL: <http://emc.medicines.org.uk/>

Nexium® IV (AstraZeneca)

Esomeprazole

Pharmaceutical form: 40mg powder solution for injection or infusion

Nexium® IV is indicated for gastric antisecretory treatment when the oral route is not possible. These include gastroesophageal reflux disease in patients with oesophagitis and healing and prevention of gastric ulcers associated with NSAID therapy. It is contraindicated in cases of hypersensitivity to esomeprazole or other substituted benzimidazoles or excipients and concomitant administration with atazanavir. Esomeprazole, the S-isomer of omeprazole, is a specific inhibitor of the gastric proton pump in the parietal cells in order to decrease gastric acid secretion. Some common undesirable effects include abdominal pain, flatulence and headache. ¹

Reference

1. Medicines Authority [online]. 2008 [cited 2008 August 12]; Available from: URL: http://www.medicinesauthority.gov.mt/products/SPC_MA046%2000703_Nexium%20IV%2040mg_Powder%20for%20solution%20for%20injection%20or%20infusion_Esomeprazole%2040mg_AstraZeneca%20AB_Sweden_PoM_A02BC05_08.02.07.pdf

OncoTICE® (N.V.Organon)

Tice BCG

Pharmaceutical form: 12.5mg powder for instillation fluid for intravesical use

OncoTICE® is a freeze-dried preparation containing attenuated bacilli of Mycobacterium bovis, prepared from a culture of Bacillus Calmette-Guérin. It is indicated for treatment of primary or concurrent carcinoma-in-situ of the urinary bladder and for prophylaxis of recurrence of high grade and/or relapsing superficial papillary transitional cell carcinoma of the urinary bladder after transurethral resection. It is only recommended for stage

Ta grade 1 papillary tumours, when there is a high risk of tumour recurrence. It is contraindicated in urinary tract infection, gross haematuria, pregnancy and lactation, active tuberculous infection, positive HIV serology and impaired immune response. The adverse effects are generally mild and transient; most commonly include pollakiuria, dysuria and influenza-like illness.¹

Reference

1. Medicines.org.uk. Electronic Medicines Compendium [online]. 2008 [cited 2008 September 14]; Available from: URL: <http://emc.medicines.org.uk/>

Pregnyl® (N V Organon)

Gonadotrophin

Pharmaceutical form: 5000IU powder for solution for injection

It is indicated for hypogonadotrophic hypogonadism, delayed puberty due to insufficient gonadotrophic pituitary function and sterility in the male. In the female, it is indicated for sterility due to the absence of follicle-ripening or ovulation. In conjunction with HMG, it is indicated in the promotion of controlled superovulation in the medically assisted reproduction programmes. Pregnyl® stimulates the steroidogenesis by virtue of a biological effect similar to that of leutinising hormone. In the male it promotes the production of testosterone and in the female the production of estrogens and particularly of progesterone after ovulation. It is contraindicated in vaginal bleeding with unknown cause, pregnancy and lactation, breast, uterine, ovarian, testicular tumours and uncontrolled non-gonadal endocrinopathies. It is also contraindicated in known or suspected androgen-dependent tumours and hypersensitivity cases. Undesirable effects include oedema, headache, severe ovarian hyperstimulation syndrome and gynaecomastia.¹

Reference

1. Medicines.org.uk. Electronic Medicines Compendium [online]. 2008 [cited 2008 September 12]; Available from: URL: <http://emc.medicines.org.uk/>

Rinialer® (Laboratorios Bial)

Rupatadine

Pharmaceutical form: 10mg tablet

Rupatadine is a second generation, long acting antihistamine with selective peripheral H₁-receptor

antagonist activity. Its metabolites particularly desloratadine and its hydroxylated metabolites have an antihistaminic activity and may partially contribute to the overall efficacy of the drug. It is indicated for allergic rhinitis and chronic idiopathic urticaria in adults and adolescents over 12 years. The most common adverse effects in clinical trials were somnolence, headache, fatigue, asthenia, dry mouth and dizziness.¹

Reference

1. Medicines Authority [online]. 2008 [cited 2008 August 12]; Available from: URL: http://www.medicinesauthority.gov.mt/products/SPC_MA004%2000601_Rinialer_Tablet_Rupatadine%2010mg_Laboratorios%20Bial%20%20Portela%20&%20Ca.%20S.A._Portugal_PoM_R06AX_28_23.08.07.pdf

Suboxone® (SP Europe)

Buprenorphine/naloxone

Pharmaceutical form: 2mg/0.5mg powder for oral or rectal suspension

Suboxone® is used as a substitution treatment for opioid drug dependence in adults and adolescents over 15 years. The naloxone component is important to help discourage diversion and misuse whilst buprenorphine reduces patients' opioid craving and withdrawal symptoms. It is contraindicated in the case of hypersensitivity to active ingredient or excipients, severe respiratory insufficiency, severe hepatic insufficiency, acute alcoholism or delirium tremens. Some adverse effects include headache, pain and withdrawal syndrome.¹

Reference

1. European Medicines Agency. EPARs for authorised medicinal products for human use [online]. 2008 January 22 [cited 2008 August 9]; Available from: URL: <http://www.emea.europa.eu/humandocs/Humans/EPAR/suboxone/suboxone.htm>

Vicombil® (Laboratorios Bial)

Retinol, ergocalciferol, tocopherol, thiamine, riboflavin, pyridoxine, cyanocobalamin, ascorbic acid, nicotinamide, folic acid, calcium pantothenate

Pharmaceutical form: syrup

Vicombil® is a multivitamin formulation used as a supplement when an inadequate intake of vitamins is evident. However it is contraindicated in hypervitaminosis and hypersensitivity to any of the vitamins. It is important that the recommended dosage is not exceeded. If

overdosage occurs, signs of hypervitaminosis A and D will develop.¹

Reference

1. Medicines Authority [online]. 2008 [cited 2008 August 12]; Available from: URL: http://www.medicinesauthority.gov.mt/products/SPC_MA004%200501_Vicombil_Syrup_Refer%20to%20SmPC_Laboratorios%20Bial%20%20Portela%20&%20Ca.%20S.A._Portugal_OTC_A11JC_28.12.06.pdf

Wellbutrin® XR (Glaxo Group)

Bupropion Hydrochloride

Pharmaceutical form: 150mg modified release tablet

Bupropion is a selective inhibitor of the neuronal re-uptake of catecholamines. It has a minimal effect on the re-uptake of indolamines but does not inhibit either monoamine oxidase. It is indicated for the treatment of major depressive episodes. Patients taking other medicines containing bupropion should not take Wellbutrin® as the incidence of seizures is dose dependent. It is also contraindicated in patients with a history or current seizure disorder and patients with known central nervous system tumour. Other contraindications include hypersensitivity to any of its ingredients, patients with severe hepatic cirrhosis, current or previous diagnosis of bulimia or anorexia nervosa, patients who are undergoing abrupt withdrawal from alcohol or medicines associated with risk of seizures on withdrawal at any time during treatment and concomitant

use with monoamine oxidase inhibitors. Some common adverse effects include insomnia, headache, dry mouth and gastrointestinal disturbance such as nausea and vomiting.¹

Reference

1. Medicines Authority [online]. 2008 [cited 2008 August 12]; Available from: URL: http://www.medicinesauthority.gov.mt/products/SPC_MA302%2000101_Wellbutrin@%20XR_Modified%20release%20tablet_Bupropion%20Hydrochloride%20150mg_Glaxo%20Group%20Ltd._United%20Kingdom_PoM_N07BA02_20.08.07.pdf

Xylo-POS® (Ursapharm Arzneimittel)

Xylometazoline Hydrochloride

Pharmaceutical form: 1mg/ml nasal spray solution

It is indicated to relief nasal congestion and runny nose caused by colds and flu, rhinitis, sinusitis and hayfever. Xylometazoline is a sympathomimetic agent that acts quickly to reduce congestion. It is contraindicated in hypersensitivity and patients with trans-sphenoidal hypophysectomy or surgery exposing the dura mater. The side effects that occasionally occur include local burning sensation, dryness or irritation of nasal mucosa, nausea and headache.¹

Reference

1. ENT Technologies Pty Ltd. ENT Technologies [online]. 2005 [cited 2008 August 14]; Available from: URL: http://www.enttech.com.au/prod_flo_xylo_pos.shtml

Variations in summary of product characteristics of medicinal products available locally

From December 2007 till May 2008, the following variations (Type II variations) have been included in the summary of products characteristics of medicinal products available locally as accepted by the European Medicines Agency.

Avandamet®

Active Ingredient: Rosiglitazone maleate and metformin hydrochloride

Variation: A new warning has been added which stated that rosiglitazone was associated with an increased risk of myocardial ischaemic events. The use of rosiglitazone in patients with ischaemic heart disease and/or peripheral arterial disease particularly in those with myocardial ischaemic symptoms is not recommended.

A contraindication was also added which states that rosiglitazone must not be used in patients with an acute coronary syndrome since the medicine has not been studied in controlled trials in this specific patient group.

When rosiglitazone is used in combination with insulin, an increased incidence of cardiac failure has been observed in clinical trials. Insulin and rosiglitazone are both associated with fluid retention. Thus, concomitant administration may increase the risk of oedema and could increase the risk of ischaemic heart disease. Insulin should only be added to established rosiglitazone therapy in exceptional cases and under close supervision.¹

Reference

1. European Medicines Agency. EPARs for authorised medicinal products for human use. [online]. 2008 June 17 [cited 2008 August 22]; Available from: URL: <http://www.emea.europa.eu/humandocs/Humans/EPAR/avandamet/avandamet.htm>

Avandia®

Active Ingredient: Rosiglitazone

Variation: Treatment with rosiglitazone may be associated with an increased risk of myocardial ischaemic events.

Therefore its use in patients with ischaemic heart disease and/or peripheral arterial disease is not recommended. In addition, rosiglitazone is contraindicated in patients with acute coronary syndrome as this drug has not been studied in this specific patient group in controlled trials.¹

Reference

1. European Medicines Agency. EPARs for authorised medicinal products for human use. European [online]. 2008 July 15 [cited 2008 September 8]; Available from: URL: <http://www.emea.europa.eu/humandocs/Humans/EPAR/avandia/avandia.htm>

Avastin®

Active Ingredient: Bevacizumab

Variation: The indication of Avastin® was extended to include its use in combination with interferon alfa-2a for first line treatment of patients with advanced and/or metastatic renal cell cancer and in combination with fluoropyrimidine-based chemotherapy for patients with metastatic carcinoma of the colon or rectum.

The pharmacokinetics of bevacizumab was studied in a limited number of paediatric patients. It suggested that the volume of distribution and clearance of bevacizumab were comparable to that in adults with solid tumours. The safety and efficacy in children and adolescents have not been established so its use is not recommended.

An open-label, randomised, active controlled, multicentre clinical trial evaluated Avastin® in combination with weekly paclitaxel for locally recurrent or metastatic breast cancer in patients who had not previously received chemotherapy for locally recurrent and metastatic disease. Although the treatment effects remains unchanged as

measured by hazard ratios, the absolute numbers of the median progression free survival and response rates have changed.

In post-marketing setting, pulmonary hypertension was reported. The incidence of venous thromboembolic events in clinical trials was similar in patients receiving Avastin[®] in combination with chemotherapy compared to those receiving the control chemotherapy alone. Venous thromboembolic events include deep venous thrombosis, pulmonary embolism and thrombophlebitis.¹

Reference

1. European Medicines Agency. EPARs for authorised medicinal products for human use. European [online]. 2008 March 7 [cited 2008 September 14]; Available from: URL: <http://www.emea.europa.eu/humandocs/Humans/EPAR/avastin/avastin.htm>

Axura[®]

Active Ingredient: Memantine hydrochloride

Variation: Five clinical studies in patients with Alzheimer's disease showed that no relevant differences were observed when they were treated with memantine 20mg once-daily as compared with 10mg bid. Pharmacokinetic data obtained from healthy subjects showed minimal differences in the plasma concentration-time profile between the two dosing regimens. Both regimens have showed similar safety profile.¹

Reference

1. European Medicines Agency. EPARs for authorised medicinal products for human use. European [online]. 2008 May 30 [cited 2008 September 8]; Available from: URL: <http://www.emea.europa.eu/humandocs/Humans/EPAR/axura/axura.htm>

Betaferon[®]

Active Ingredient: Interferon beta-1b

Variation: After an integrated analysis of two year placebo controlled, randomised study in patients with a single demyelinating event and the first-year of the open label following study showed that there is no evidence for benefit in terms of confirmed disability progression in the majority of patients receiving 'immediate' treatment.

Confirmed disability progression occurred in 24% of patients in delayed treatment group and 16% in the immediate treatment group. The patients' follow-up is still going on to provide additional data. No benefit in quality of life which was attributed to Betaferon[®] has been observed.¹

Reference

1. European Medicines Agency. EPARs for authorised medicinal products for human use. European [online]. 2008 January 24 [cited 2007 September 10]; Available from: URL: <http://www.emea.europa.eu/humandocs/Humans/EPAR/betaferon/betaferon.htm>

Caelyx[®]

Active Ingredient: Doxorubicin hydrochloride (pegylated liposomal)

Variation: The indication was extended to include the use of bortezomib in combination for the treatment of progressive multiple myeloma in patients who have received at least one prior therapy and who have already undergone or are unsuitable for bone marrow transplant.¹

Reference

1. European Medicines Agency. EPARs for authorised medicinal products for human use. [online]. 2008 March 7 [cited 2008 August 22]; Available from: URL: <http://www.emea.europa.eu/humandocs/Humans/EPAR/caelyx/caelyx.htm>

CellCept[®]

Active Ingredient: Mycophenolate

Variation: Cases of Progressive Multifocal Leukoencephalopathy (PML) have been reported by patients receiving CellCept[®]. These were sometimes fatal. However, the contributory role of CellCept[®] cannot be excluded. The reported cases generally had risk factors for PML, including immunosuppressant therapies and impairment of immune function. Thus, in immunosuppressed patients, physicians should consider PML in the differential diagnosis in patients reporting neurological symptoms and consultation with a neurologist should be considered as clinically indicated. Furthermore, in patients who develop PML, physicians should consider the reduction of the total immunosuppression. In transplant

patients reduced immunosuppressant may place the graft at risk.

Since CellCept® has been first marketed, 38 cases of spontaneous abortion from 191 pregnancy cases have occurred. Its use is not recommended during pregnancy and should be reserved for cases where no more suitable alternative treatment is available.¹

Reference

1. European Medicines Agency. EPARs for authorised medicinal products for human use. European [online]. 2008 March 12 [cited 2008 August 26]; Available from: URL: <http://www.emea.europa.eu/humandocs/Humans/EPAR/cellcept/cellept.htm>

Champix®

Active Ingredient: Varenicline tartrate

Variation: A warning was included that depressed mood may be a symptom of nicotine withdrawal. Depression rarely including suicidal ideation and suicide attempt, has been reported in patients undergoing smoking cessation attempt. These symptoms have also been reported while attempting to quit smoking with varenicline. Clinicians should be aware of the possible emergence of significant depressive symptomatology in patients undergoing a smoking cessation attempt and should advise patients accordingly.¹

Reference

1. European Medicines Agency. EPARs for authorised medicinal products for human use. European [online]. 2008 April 14 [cited 2008 September 11]; Available from: URL: <http://www.emea.europa.eu/humandocs/Humans/EPAR/champix/champix.htm>

Cialis®

Active Ingredient: Tadalafil

Variation: Twenty-two cases of convulsions were identified. Eight of which had a history of epilepsy and another two had a second fit after discontinuation of tadalafil. In another eight cases, convulsions occurred within 24 hours after the last tadalafil dose.

In post-marketing surveillance, twenty-four cases of amnesia were reported. Some of these patients had other risk factors. This case suggests causal relationship.

Transient amnesia and seizures are added to the undesirable effects list.

Sudden decrease or loss of hearing has been reported in a small number of post-marketing and clinical trial cases with the use of all PDE5 inhibitors, including tadalafil. The CHMP requested a cumulative review of such cases. After review, sudden deafness was included in the adverse effects list.¹

Reference

1. European Medicines Agency. EPARs for authorised medicinal products for human use. European [online]. 2008 August 5 [cited 2008 September 8]; Available from: URL: <http://www.emea.europa.eu/humandocs/Humans/EPAR/cialis/cialis.htm>

Feriprox®

Active Ingredient: Deferiprone

Variation: The adverse effects headache and fatigue are added to the list; both with a frequency set as common. Both the incidence of agranulocytosis and neutropenia have been amended to common.¹

Reference

1. European Medicines Agency. EPARs for authorised medicinal products for human use. European [online]. 2008 May 7 [cited 2007 September 11]; Available from: URL: <http://www.emea.europa.eu/humandocs/Humans/EPAR/feriprox/feriprox.htm>

Forsteo®

Active Ingredient: Teriparatide

Variation: The therapeutic indications are extended to include treatment of osteoporosis associated with sustained systemic glucocorticoid therapy in women and men at increased risk of fracture.

Increased alkaline phosphatase (ALP) is added to the adverse effects list in the “uncommon” frequency category. In a cumulative review, 175 medically confirmed spontaneous cases of increased alkaline phosphatase have been identified. Only 8 serious cases occurred. Of the 175 cases, 39 cases reported concurrent disease states associated with increased ALP levels and in 38 cases concomitant medication has been reported that may be associated with hepatotoxicity. Many cases did not contain

sufficient information to assess for confounding factors. The ALP value was provided in 117 cases. The majority of cases had no elevation or mild elevation of ALP. ALP was considered to be moderately to severely increase in 14 cases. Of these 14 cases, 5 patients recovered after stopping teriparatide and 3 patients recovered or were recovering while continuing teriparatide therapy.¹

Reference

1. European Medicines Agency. EPARs for authorised medicinal products for human use. European [online]. 2008 June 16 [cited 2008 September 8]; Available from: URL: <http://www.emea.europa.eu/humandocs/Humans/EPAR/ferriprox/ferriprox.htm>

Humira®

Active Ingredient: Adalimumab

Variation: The indication was extended to include treatment of adult patients with moderate to severe chronic plaque psoriasis or active and progressive psoriatic arthritis when the response to previous drug therapy was inadequate. Humira® has shown to reduce the rate of progression of peripheral joint damage and to improve physical function.¹

Reference

1. European Medicines Agency. EPARs for authorised medicinal products for human use. European [online]. 2008 February 19 [cited 2008 August 27]; Available from: URL: <http://www.emea.europa.eu/humandocs/Humans/EPAR/humira/humira.htm>

Infanrix Hexa®

Active Ingredient: Diphtheria toxoid adsorbed, tetanus toxoid adsorbed, pertussis toxoid adsorbed, filamentous haemagglutinin adsorbed, pertactin adsorbed, recombinant Hepatitis B surface antigen adsorbed, inactivated poliovirus types 1, 2, 3, conjugate of *Haemophilus influenzae* type b capsular polysaccharide and tetanus toxoid adsorbed.

Variation: Due to a potential risk of apnoea, there is the need for respiratory monitoring for 48-72 hours when the primary immunisation series is administered to very premature infants (born ≤ 28 weeks of gestation) and especially those with a previous history of respiratory immaturity. However, preterm infants should not be

withdrawn from the immunisation scheme because the benefit of vaccination outweighs the risk of apnoea.¹

Reference

1. European Medicines Agency. EPARs for authorised medicinal products for human use. European [online]. 2008 May 8 [cited 2008 September 8]; Available from: URL: <http://www.emea.europa.eu/humandocs/Humans/EPAR/infanrixhexa/infanrixhexa.htm>

Intron®A

Active Ingredient: Interferon alfa-2b

Variation: Eleven cases of Vogt-Koyanagi-Harada (VKH) syndrome associated with interferon alfa therapy were identified in a cumulative review. This syndrome is a granulomatous inflammatory disorder affecting the eyes, auditory system, meninges and skin. The role of the active ingredient cannot be totally ruled out in all cases but today it is well known that Hepatitis C infection can be itself involved in the development of auto-immune disorders. If VKH syndrome is suspected, antiviral treatment should be withdrawn and corticosteroid therapy discussed.

Two studies were conducted in patients co-infected with HIV and HCV. This showed that patients who received peglyated interferon alfa-2b with ribavirin responded more than patients who received standard interferon alfa-2b with ribavirin.¹

Reference

1. European Medicines Agency. EPARs for authorised medicinal products for human use [online]. 2008 May 27 [cited 2008 September 7]; Available from: URL: <http://www.emea.europa.eu/humandocs/Humans/EPAR/intronA/intronA.htm>

Invega™

Active Ingredient: Paliperidone

Variation: A drug interaction study between paliperidone and carbamazepine have showed that co-administration of Invega™ once daily with carbamazepine 200mg twice daily caused a decrease of approximately 37% in the mean steady-state C_{max} and AUC of paliperidone. This decrease is caused, to a substantial degree, by an increase in renal clearance of paliperidone probably as a result of induction of renal P-gp by carbamazepine. A minor decrease in the

amount of drug excreted unchanged in the urine suggested that there was little effect on the CYP metabolism or bioavailability of paliperidone. Large decrease in plasma concentrations of paliperidone could occur with higher doses of carbamazepine.

On initiation and discontinuation of carbamazepine, the dose of Invega™ should be re-evaluated and increased if necessary. It takes 2-3 weeks for full induction to be achieved and upon discontinuation of the inducer, the effect wears off over a similar time period. Other medicinal products or herbals which are inducers such as rifampicin and St John's wort may have similar effects on paliperidone.¹

Reference

1. European Medicines Agency. EPARs for authorised medicinal products for human use. European [online]. 2008 June 9 [cited 2008 September 8]; Available from: URL: <http://www.emea.europa.eu/humandocs/Humans/EPAR/invega/invega.htm>

Januvia™

Active Ingredient: Sitagliptin

Variation: The indications for Januvia™ were extended to include a dual oral combination of sitagliptin with a sulphonylurea and to add a triple oral combination indication of sitagliptin with metformin and a sulphonylurea.

A 24 week placebo-controlled factorial clinical study of initial therapy with the combination of sitagliptin and metformin, significant improvement in HbA1c compared to placebo were observed for sitagliptin 50mg b.i.d with metformin 500mg b.i.d and sitagliptin 50mg b.i.d with metformin 1000mg b.i.d. Relative to monotherapy, combination therapy also provided significant improvement in glycaemic parameters. The decrease in body weight with the combination of sitagliptin and metformin was similar to that observed with metformin alone or placebo; there was no change from baseline from patients on sitagliptin alone. The overall incidence of adverse reactions considered as drug-related in patients

treated with the combination of sitagliptin and metformin compared to patients treated with placebo was 14.0% and 9.7%, respectively. The overall incidence of adverse reactions considered as drug-related in patients treated with the combination of sitagliptin and metformin was comparable to metformin alone and greater than sitagliptin alone, with the differences relative to sitagliptin alone primarily due to gastrointestinal adverse reactions.

Postmarketing reports of serious hypersensitivity reactions in patients treated with sitagliptin were reported. These included anaphylaxis, angioedema and exfoliative skin conditions including Stevens-Johnson syndrome. The onset of these reactions occurred within the first 3 months after the start of treatment with sitagliptin, with some reports occurring after the first dose. If a hypersensitivity reaction is suspected, discontinue sitagliptin, assess for other potential causes for the event and institute alternative treatment for diabetes.¹

Reference

1. European Medicines Agency. EPARs for authorised medicinal products for human use. European [online]. 2008 May 29 [cited 2008 September 8]; Available from: URL: <http://www.emea.europa.eu/humandocs/Humans/EPAR/januvia/januvia.htm>

Keppra®

Active Ingredient: Levetiracetam

Variation: An in vitro induction study in cultured human hepatocytes was conducted to assess the effect of levetiracetam on enzyme induction and hepatic drug metabolizing enzyme activities. It was shown that in vitro levetiracetam and its primary metabolite do not inhibit the major human liver cytochrome P450 isoforms, glucuronyl transferase and epoxide hydroxylase activities. In addition, levetiracetam does not affect the in vitro glucuronidation of valproic acid.

Levetiracetam had little or no effect on CYP1A2, SUL1E1 or UGT1A1, in human hepatocytes in culture but caused mild induction of CYP2B6 and CYP3A4. The in vitro data and in vivo interaction data on oral contraceptives, digoxin and warfarin indicate that no

significant enzyme induction is expected in vivo. So, the interaction of Keppra® with other substances, or vice versa, is unlikely.¹

Reference

1. European Medicines Agency. EPARs for authorised medicinal products for human use. European [online]. 2008 January 24 [cited 2008 September 8]; Available from: URL: <http://www.emea.europa.eu/humandocs/Humans/EPAR/keppra/keppra.htm>

Levitra®

Active Ingredient: Vardenafil

Variation: Sudden decrease or loss of hearing has been reported in a small number of post-marketing and clinical trial cases with the use of all PDE5 inhibitors, including vardenafil. The CHMP requested a cumulative review of such cases. After review, sudden deafness was included in the adverse effects list.¹

Reference

1. European Medicines Agency. EPARs for authorised medicinal products for human use. European [online]. 2008 August 19 [cited 2008 September 8]; Available from: URL: <http://www.emea.europa.eu/humandocs/Humans/EPAR/levitra/levitra.htm>

MicardisPlus®

Active Ingredient: Telmisartan and hydrochlorothiazide

Variation: A new strength of MicardisPlus® (80mg telmisartan/25mg hydrochlorothiazide) is added. The CHMP considered that the risk-benefit balance of the new strength of the MicardisPlus® fixed dose combination in the treatment of essential hypertension indicated in patients whose blood pressure is not adequately controlled on MicardisPlus® 80mg/12.5mg or patients who have been previously stabilised on telmisartan and hydrochlorothiazide given separately was favourable.¹

Reference

1. European Medicines Agency. EPARs for authorised medicinal products for human use. [online]. 2008 July 24 [cited 2008 August 29]; Available from: URL: <http://www.emea.europa.eu/humandocs/Humans/EPAR/micardisplus/micardisplus.htm>

Mirapexin®

Active Ingredient: Pramipexole

Variation: Some adverse effects frequencies were amended:

<u>Adverse reaction</u>	<u>Frequency</u>	<u>Pramipexole N=1923 (%)</u>
hypotension	very common	12.6
hallucinations	common	6.6
dizziness	very common	15.5
abnormal dreams	common	3.5
insomnia	common	8.2
oedema	peripheral common	1.9

Dopamine agonists, especially at high doses for Parkinson’s disease have been reported to increase libido and hypersexuality, generally reversible upon reduction of the dose or treatment discontinuation. It also causes allergic reactions like hypersensitivity, rash and pruritus.¹

Reference

1. European Medicines Agency. EPARs for authorised medicinal products for human use. European [online]. 2008 May 29 [cited 2008 August 11]; Available from: URL: <http://www.emea.europa.eu/humandocs/Humans/EPAR/mirapexin/mirapexin.htm>

Mircera®

Active Ingredient: Methoxy polyethylene glycol-epoetin beta

Variation: A class safety review by the PhVWP and the CHMP was initiated as recent data showed a consistent unexplained excess mortality in cancer patients and patients with chronic kidney disease treated with epoetins for anaemia. Relatively high target haemoglobin concentration may be associated with an increase in the risk of mortality and cardiovascular morbidity. As a result, epoetins should only be used if associated with symptoms and a uniform target haemoglobin range for all epoetins must be established.

Results of a clinical study report on the effect of severe hepatic impairment on the pharmacokinetics of Mircera® showed that no adjustments of the starting dose nor of the dose modification rules are required. In a single dose study, after IV administration, the pharmacokinetics of

Mircera® are similar in patients with severe hepatic impairment as compared to healthy subjects.¹

Reference

1. European Medicines Agency. EPARs for authorised medicinal products for human use. European [online]. 2008 May 16 [cited 2008 September 10]; Available from: URL: <http://www.emea.europa.eu/humandocs/Humans/EPAR/mircera/mircera.htm>

Neoclaritin™

Active Ingredient: Desloratadine

Variation: The indication was extended from 'chronic idiopathic urticaria' to 'urticaria'.¹

Reference

1. European Medicines Agency. EPARs for authorised medicinal products for human use. European [online]. 2008 August 11 [cited 2008 September 8]; Available from: URL: <http://www.emea.europa.eu/humandocs/Humans/EPAR/neoclaritin/neoclaritin.htm>

Orgalutran®

Active Ingredient: Ganirelix

Variation: A warning on tubal abnormalities and the incidence of ectopic pregnancies was included. The incidence of ectopic pregnancies might be increased in infertile women undergoing assisted reproduction, particularly IVF as these often suffer from tubal abnormalities. Therefore an early ultrasound confirmation of an intrauterine pregnancy is important.¹

Reference

1. European Medicines Agency. EPARs for authorised medicinal products for human use. European [online]. 2008 February 29 [cited 2008 September 11]; Available from: URL: <http://www.emea.europa.eu/humandocs/Humans/EPAR/orgalutran/orgalutran.htm>

PegIntron™

Active Ingredient: Interferon alfa-2b

Variation: Eleven cases of Vogt-Koyanagi-Harada (VKH) syndrome associated with interferon alfa therapy were identified in a cumulative review. This syndrome is granulomatous inflammatory disorder affecting the eyes, auditory system, meninges and skin. The role of the active ingredient cannot be totally ruled out in all cases but today it is well known that Hepatitis C infection can be itself

involved in the development of auto-immune disorders. If VKH syndrome is suspected, antiviral treatment should be withdrawn.

A multicenter, long-term follow-up study of subjects with chronic hepatitis C (HCV) who had been treated in a prior study with peginterferon alfa-2b (with or without ribavirin) was aimed to assess the durability of virologic response and to assess HCV disease progression. Overall the results of the study confirm the durability of the virologic response up to 5 years. The likelihood of maintaining virologic response over 5 years in subjects who initially achieved a sustained response is 99%. However, this does not preclude the occurrence of hepatic events in patients with cirrhosis.

Pivotal studies conducted in HIV/HCV co-infected patients together with published data consistently show a higher risk of anaemia when ribavirin and zidovudine are coadministered. Thus, concomitant use of ribavirin and zidovudine is not recommended.¹

Reference

1. European Medicines Agency. EPARs for authorised medicinal products for human use. European [online]. 2008 June 2 [cited 2008 September 16]; Available from: URL: <http://www.emea.europa.eu/humandocs/Humans/EPAR/pegintron/pegintron.htm>

Prevenar™

Active Ingredient: Pneumococcal saccharide conjugated vaccine, absorbed

Variation: Due to a potential risk of apnoea, there is the need for respiratory monitoring for 48-72 hours when the primary immunization series is administered to very premature infants (≤ 28 weeks of gestation) especially those with a previous history of respiratory immaturity. Vaccination should not be withheld or delayed as the benefit of the vaccination is high in these infants.

Reference

1. European Medicines Agency. EPARs for authorised medicinal products for human use. European [online]. 2008 April 25 [cited 2008 July 22]; Available from: URL: <http://www.emea.europa.eu/humandocs/Humans/EPAR/prevenar/prevenar.htm>

Prezista™

Active Ingredient: Darunavir

Variation: Two toxicity studies suggested that the exposure in rats aged 5-11 days is higher than in adult rats but then it becomes comparable to adult rats after 23 days of age. The high exposure at young age and the subsequent decrease in exposure from the eight day of life onwards is probably related to the maturation of the liver metabolizing enzymes and the blood brain barrier. The presented preclinical results suggest that comparable doses may cause a higher exposure in very young children compared to adults, which may result in a higher risk of toxicity.

The final study report describing the pharmacokinetics and safety of darunavir with low-dose ritonavir in patients with mild and moderate hepatic impairment confirmed the concentration-dependent protein binding (AAG) of darunavir. The increase in free fraction of AAG is not considered as an issue for the efficacy, however safety may be affected. Therefore, darunavir should be used with caution in patients with mild or moderate impaired hepatic function. The free fraction of darunavir may be increased in patients with mild to moderate hepatic dysfunction due to lower AAG.¹

Reference

1. European Medicines Agency. EPARs for authorised medicinal products for human use. European [online]. 2008 July 7 [cited 2008 July 22]; Available from: URL: <http://www.emea.europa.eu/humandocs/Humans/EPAR/prezista/prezista.htm>

Protelos®

Active Ingredient: Strontium ranelate

Variation: Following a total of around 570,000 patient-years of worldwide exposure, 16 cases of severe hypersensitivity syndromes including, in particular, drug rash with eosinophilia and systemic symptoms (DRESS) in patients treated with Protelos®, two of which were fatal, have been reported. DRESS is a serious and life-threatening condition with the time to onset was usually around 3-6 weeks. The outcome in most cases is favourable upon discontinuation of Protelos® and after

initiation of corticosteroid therapy. Patients should be informed to stop it immediately and permanently when a rash occurs and to seek medical advice. Musculoskeletal pain including muscle spasm, myalgia, bone pain, arthralgia and pain in extremity was also added to the undesirable effects list.¹

Reference

1. European Medicines Agency. EPARs for authorised medicinal products for human use. European [online]. 2008 February 20 [cited 2008 August 20]; Available from: URL: <http://www.emea.europa.eu/humandocs/Humans/EPAR/protelos/protelos.htm>

Rapamune®

Active Ingredient: Sirolimus

Variation: In a study performed to evaluate the pharmacokinetics of sirolimus in severe hepatic impairment showed longer half-lives, larger exposure and lower clearances. These trends were much more pronounced than those previously observed in patients with mild to moderate hepatic impairment. Thus, it is recommended that the maintenance dose be reduced by approximately one half in patients with severe hepatic impairment but there is no need to modify the loading dose. Furthermore, therapeutic drug monitoring after a loading dose or a change of dose should be performed for a prolonged period of time in these patients until stable concentrations are reached.¹

Reference

1. European Medicines Agency. EPARs for authorised medicinal products for human use. European [online]. 2008 July 10 [cited 2008 September 8]; Available from: URL: <http://www.emea.europa.eu/humandocs/Humans/EPAR/viagra/viagra.htm>

Rebetol®

Active Ingredient: Ribavirin

Variation: A multicenter, long-term follow-up study of subjects with chronic hepatitis C (HCV) who had been treated in a prior study with peginterferonalfa-2b (with or without ribavirin) was aimed to assess the durability of virologic response and to assess HCV disease progression. Overall the results of the study confirm the durability of the virologic response up to 5 years. The likelihood of

maintaining virologic response over 5 years in subjects who initially achieved a sustained response is 99%. However, this does not preclude the occurrence of hepatic events in patients with cirrhosis.

Pivotal studies conducted in HIV/HCV coinfecting patients together with published data consistently show a higher risk of anaemia when ribavirin and zidovudine are co administered. Thus, concomitant use of ribavirin and zidovudine is not recommended.¹

Reference

1. European Medicines Agency. EPARs for authorised medicinal products for human use. [online]. 2008 June 2 [cited 2008 August 21]; Available from: URL: <http://www.emea.europa.eu/humandocs/Humans/EPAR/rebetol/rebetol.htm>

Remicade®

Active Ingredient: Infliximab

Variation: On the basis of a review of data from post-marketing experience, the adverse effects section was updated to include interstitial lung disease and rapidly progressive interstitial lung disease. It was sorted in a table irrespective of its origin such as clinical trials. The frequency of events were re-organised and arranged in order of decreasing seriousness.

Analysis of clinical studies on subjects with ulcerative colitis from baseline through 54 weeks, demonstrated a reduction of the condition related hospitalisations and surgical procedures with infliximab treatment. The number of ulcerative colitis-related hospitalisations and surgical procedures were lower in the 5 and 10 mg/kg infliximab treatment groups than in the placebo group. Fewer subjects have undergone colectomy in infliximab group than in the placebo group.¹

Reference

1. European Medicines Agency. EPARs for authorised medicinal products for human use. [online]. 2008 July 22 [cited 2008 September 8]; Available from: URL: <http://www.emea.europa.eu/humandocs/Humans/EPAR/remicade/remicadeM2.htm>

Rotarix®

Active Ingredient: Human rotavirus, live attenuated

Variation: Due to a potential risk of apnoea, there is the need for respiratory monitoring for 48-72 hours when the primary immunisation series is administered to very premature infants (born ≤ 28 weeks of gestation) especially those with a previous history of respiratory immaturity. Vaccination should not be withheld or delayed as the benefit of the vaccination is high in this group of infants.¹

Reference

1. European Medicines Agency. EPARs for authorised medicinal products for human use. European [online]. 2008 February 5 [cited 2008 September 16]; Available from: URL: <http://www.emea.europa.eu/humandocs/Humans/EPAR/rotarix/rotarix.htm>

Twinrix Adult®/Twinrix Paediatric®

Active Ingredient: Inactivated hepatitis A, hepatitis B recombinant, adsorbed vaccine

Variation: After analysis of pooled safety data from 24 clinical trials and post-marketing surveillance, the adverse events reported and the frequency of some adverse events were updated. A distinction was made between adverse events occurring during clinical trials and post-marketing surveillance. Among the changes, hypoaesthesia, lichen planus or muscle weakness were added to the list of adverse effects whilst syncope has been removed since the latter is attributed to the injection rather than to the vaccine itself.

During the post-marketing surveillance, cases of overdose have been reported. The adverse events reported after overdose are similar to those reported with normal vaccine administration.^{1,2}

Reference

1. European Medicines Agency. EPARs for authorised medicinal products for human use [online]. 2008 July 9 [cited 2008 September 10]; Available from: URL: <http://www.emea.europa.eu/humandocs/Humans/EPAR/twinrixadult/twinrixadult.htm>
2. European Medicines Agency. EPARs for authorised medicinal products for human use. European [online]. 2008 July 9 [cited 2008 September 10]; Available from: URL: <http://www.emea.europa.eu/humandocs/Humans/EPAR/twinrixpaediatric/twinrixpaediatric.htm>

Velcade®

Active Ingredient: Bortezomib

Variation: A contraindication was added to include acute diffuse infiltrative pulmonary and pericardial disease due to rare reports of such diseases of unknown origin in patients receiving Velcade®. A pretreatment chest radiograph is recommended to determine if any additional diagnostic measures are necessary and to serve as a baseline for potential post-treatment pulmonary changes. In the case of new or worsening pulmonary symptoms a prompt diagnostic evaluation should be performed.

Two drug interaction studies with CYP3A4 inhibitor and CYP2C19 inhibitor using ketoconazole and omeprazole respectively were carried out. The former showed a bortezomib AUC mean increase of 35%. The other drug-drug interaction study assessing the effect of omeprazole showed no significant effect on the pharmacokinetics of bortezomib. Patients should be closely monitored when bortezomib is given in combination with CYP3A4 inhibitors and CYP2C19 inhibitors. In the absence of drug-drug interaction studies investigating the effect of CYP3A4 inducers such as rifampicin on the pharmacokinetics of bortezomib, patients should be monitored closely.¹

Reference

1. European Medicines Agency. EPARs for authorised medicinal products for human use. European [online]. 2008 June 3 [cited 2008 July 22]; Available from: URL: <http://www.emea.europa.eu/humandocs/Humans/EPAR/velcade/velcade.htm>

Vfend®

Active Ingredient: Voriconazole

Variation: Data on randomised, controlled, open-label, 3-way crossover clinical study of 12 healthy subjects published in the literature showed that co-administration of voriconazole markedly inhibits the metabolism of alfentanil. Alfentanil is extensively metabolised, mainly by hepatic cytochrome (CYP) P4503A enzymes. Voriconazole is metabolized by and is also an inhibitor of the CYP P450 isozymes, CYP3A4, CYP2C19, and CYP2C9. Therefore, there is a theoretical concern that

concomitantly administered alfentanil and CYP3A inhibitors may exhibit clinically important drug interactions. When voriconazole is co-administered with alfentanil or other short acting opiates similar in structure to alfentanil and metabolized by CYP3A4 such as fentanyl and sufentanil, the dose of the latter should be reduced.

The contraindication of voriconazole and efavirenz co-administration was limiting the treatment options available to physicians for HIV patients with potentially life-threatening fungal infections, while available data show possible therapeutic benefit of co-administration when doses are adjusted. Efavirenz may be co-administered with voriconazole if the maintenance dose of voriconazole is increased to 400 mg every 12 hours and the efavirenz dose is reduced by 50%, i.e. to 300 mg once daily. When treatment with voriconazole is stopped, the initial dosage of efavirenz should be restored.¹

Reference

1. European Medicines Agency. EPARs for authorised medicinal products for human use. European [online]. 2008 April 28 [cited 2008 July 22]; Available from: URL: <http://www.emea.europa.eu/humandocs/Humans/EPAR/vfend/vfend.htm>

Viagra®

Active Ingredient: Sildenafil citrate

Variation: Sudden decrease or loss of hearing has been reported in a small number of post-marketing and clinical trials cases with the use of all PDE5 inhibitors, including sildenafil. The CHMP requested a cumulative review of such cases. After review, sudden deafness was included in the adverse effects list.¹

Reference

1. European Medicines Agency. EPARs for authorised medicinal products for human use. European [online]. 2008 June 20 [cited 2008 September 12]; Available from: URL: <http://www.emea.europa.eu/humandocs/Humans/EPAR/viagra/viagra.htm>

Xagrid®

Active Ingredient: Anagrelide hydrochloride

Variation: In a two year rat carcinogenicity study, non-neoplastic and neoplastic findings were observed and

related or attributed to an exaggerated pharmacological effect. Among them, the incidence of adrenal pheochromocytomas was increased relative to control in males at all dose levels ($\geq 3\text{mg/kg/day}$) and in females receiving 10mg/kg/day and above. The lowest dose in males (3mg/kg/day) corresponds to 37 times the human AUC exposure after a 1mg twice daily dose. Uterine adenocarcinomas, of epigenetic origin, could be related to an enzyme induction of CYP1 family. They were observed in females receiving 30mg/kg/day , corresponding to 572 times the human AUC exposure after a 1mg twice daily dose.

Currently, there is no clinical evidence that these findings are of relevance to human use.¹

Reference

1. European Medicines Agency. EPARs for authorised medicinal products for human use. European [online]. 2008 July 8 [cited 2008 September 12]; Available from: URL: <http://www.emea.europa.eu/humandocs/Humans/EPAR/xagrid/Xagrid.htm>

Zonegran®

Active Ingredient: Zonisamide

Variation: The CHMP requested to strengthen particular warnings and review the overall undesirable effects. Serious rashes, allergic reactions and major haematological disturbances, which very rarely can be fatal, are associated with products containing the sulphonamide group such as Zongeran®. Post-marketing data suggested that elderly patients have higher incidence of Stevens-Johnson Syndrome and Drug Induced Hypersensitivity Syndrome. In addition, the following adverse effects frequencies have been amended:¹

Insomnia	Common
Psychotic disorder (strange or unusual thoughts)	Common
Kidney stones	Uncommon

Reference

1. European Medicines Agency. EPARs for authorised medicinal products for human use. European [online]. 2008 June 15 [cited 2008 September 12]; Available from: URL: <http://www.emea.europa.eu/humandocs/Humans/EPAR/zonegran/zonegran.htm>

Contributors

Arrowpharm (Malta) Ltd
HF62, Qasam Industrijali
Hal-Far, B'Bugia BBG3000
Tel: 22298000

Charles de Giorgio Ltd.
Triq il-Kan. Karmenu Pirotta
B'Kara, BKR1114
Tel: 25600500
Fax: 25600200
E-mail: admin@charlesdegiorgio.com

Joseph Cassar Ltd
48, Mill Street,
Qormi QRM 3105
Tel: 21470228, 21470090
Fax: 21470219
E-mail: jcl@waldonet.net.mt

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